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TITLE:

Incidence and Risk Factors for ICU-related Posttraumatic Stress Disorder In Veterans and Civilians

RUNNING HEAD:

ICU-related PTSD In Veterans and Civilians

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CONTRIBUTORSHIP:

MBP, JLT, RC analyzed and interpreted the data, and drafted and critically revised the paper. JCJ, EWE, RSD, PPP designed and implemented the cohort and acquired data (Nashville), analyzed and interpreted the data, and drafted and critically revised the paper. AM, ALK acquired and interpreted the data, and drafted and critically revised the paper. TG, CGH, JCB interpreted the data, and drafted and critically revised the paper. MRE, MLW, RBG designed and implemented the cohort and acquired data (Seattle and Salt Lake City), interpreted the data, and drafted and critically revised the paper. All authors approved the final version submitted and to be published. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

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AT A GLANCE COMMENTARY:

Scientific Knowledge on the Subject

Posttraumatic stress disorder (PTSD) can occur in patients after the traumatizing events of critical illness, but the epidemiology is unclear with wide ranging estimates of one-year prevalence rates. Furthermore, pre-existing PTSD has rarely been systematically assessed in prior cohorts, which parallels the infrequent reporting and assumption of ICU-related PTSD incidence. Civilian populations have dominated the literature of PTSD after critical illness (i.e. as opposed to inclusion of the expanding and aging Veteran population), and post-ICU PTSD determinations have been primarily based on single screening instruments neither anchored to the critical illness, nor mapped to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria.

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What This Study Adds to the Field

This multicenter, prospective cohort study, which assessed pre-existing PTSD and included veterans and civilians from mixed medical and surgical ICU populations, demonstrated that around one in ten survivors experienced ICU-related PTSD (i.e. PTSD anchored to their critical illness) in the year after hospitalization. Pre-existing PTSD and depression are strong markers for ICU-related PTSD risk, and healthcare providers caring for these patients should be cognizant about the possible presence of this condition.

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4.6 ICU Management/Outcome

Rationale: The incidence and risk factors of posttraumatic stress disorder (PTSD) related to the intensive care unit (ICU) experience has not been reported in a mixed Veteran and civilian cohort.

Objectives: To describe the incidence and risk factors for PTSD related to critical illness and the ICU experience in veterans and civilians.

Methods: This is a prospective, observational, multicenter cohort enrolling adult survivors of critical illness following respiratory failure and/or shock from three Veterans Affairs and one civilian hospital. After classifying those with/without pre-existing PTSD (i.e. PTSD before hospitalization), we then assessed all subjects for ICU-related PTSD at 3- and 12-months post-hospitalization.

Measurements and Main Results: Of 255 survivors, 181 and 160 subjects were assessed for ICU-related PTSD at 3- and 12-month follow-up, respectively. A high probability of ICU-related PTSD was found in 1-8% of patients at either follow-up time points, whether assessed by PTSD Checklist-Event Specific Version score (PCL-S score $\geq$ 50) or item mapping using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). In the multivariable regression, pre-existing PTSD was independently associated with ICU-related PTSD at both 3 and 12 months ($P < 0.001$), as was pre-existing depression ($P < 0.03$), but veteran status was not a consistent independent risk factor for ICU-related PTSD (3-month $P = 0.01$, 12-month $P = 0.48$).

Conclusions: This study found around one in ten ICU survivors experienced ICU-related PTSD (i.e. PTSD anchored to their critical illness) in the year after hospitalization. Pre-existing PTSD and depression were strongly associated with ICU-related PTSD.

KEY WORDS: PTSD; Stress Disorders, Post-Traumatic; Intensive Care Unit; Veterans

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INTRODUCTION:

Posttraumatic stress disorder (PTSD) is defined as persistent difficulty processing previously experienced extreme life-threatening situations, such as combat violence, natural disasters, assault, or critical illness. An individual with PTSD may re-experience the traumatic event through persistent memories, nightmares, or flashbacks (intrusion), may try to avoid reminders of the event and demonstrate emotional "numbness" (avoidance), and/or may have sleeplessness, anger, hypervigilance, and an exaggerated response to startling events (hyperarousal) (1). Survivors of critical illness have reported PTSD symptoms months to even years after critical illness, possibly related to nightmare-like experiences, safety restraints creating communication barriers, and protective mechanical ventilation causing feelings of breathlessness and fear of imminent death (2, 3). Pre-existing psychiatric problems, including depression and prior PTSD, have a strong potential to exacerbate ICU-related PTSD (i.e. PTSD symptoms anchored to the intensive care unit experience), but the detailed assessment of prior PTSD is rarely done (4, 5) and prior PTSD remains unmeasured in many mixed population ICU studies (1, 6-8).

Studies assessing for the risk of PTSD after critical illness have reported prevalence rates ranging from 0% to 64%, depending on the population and intervention studied, the time interval between the ICU admission and assessment, and the instrument for screening or diagnosis used (e.g., Impact of Event Scale, Post-Traumatic Stress Syndrome screening tool, Posttraumatic Diagnostic Scale, PTSD checklist-event specific version [PCL-S]) (4, 5, 9-11). Most prior studies have used PTSD screening instruments rather than diagnostic instruments and have seldom mapped symptoms to the Diagnostic and Statistical Manual of Mental Disorders (DSM), which can be done using the PCL-S (6, 10-12). Even among current era studies, a 2015 meta-

analysis of over 500 ICU patients reported a 22% pooled PTSD prevalence at one-year (11), which contrasts our recently published large civilian ICU cohort showing a three-fold lower PTSD prevalence of 7% at one-year using the PCL-S instrument with DSM-IV mapping (13). Additionally, no multicenter studies have concurrently enrolled veteran and civilian patients during their critical illness, systematically evaluated them for pre-existing PTSD and traumatic life events, and followed them longitudinally to evaluate the incidence and unique risk factors for ICU-related PTSD in these potentially very different populations.

In this study using the PCL-S instrument and DSM-mapping, we describe the incidence of ICU-related PTSD risk and its underlying symptom clusters of intrusion, avoidance, and hyperarousal among veterans and civilians who had survived a critical illness. We also examine the potential pre-existing (e.g., age, prior depression, prior PTSD) and hospital (e.g., severity of illness, delirium, analgosedative exposure) risk factors for ICU-related PTSD. Some of the results of this study have been previously reported in the form of a published abstract (14) and unpublished distributed abstracts (15, 16).

METHODS

The study methods are detailed in the **Online Data Supplement**.

Study design, population, and patients

This prospective, observational, multicenter cohort study was nested within two studies with identical eligibility criteria (e.g., inclusion of those with respiratory failure and/or shock). Veteran patients were enrolled in the Measuring the Incidence and determining risk factors for Neuropsychological Dysfunction in ICU Survivors study (MIND-ICU, NCT00400062) and civilian patients were enrolled in the Bringing to Light the Risk Factors and Incidence of

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Neuropsychological Dysfunction in ICU Survivors study (BRAIN-ICU, NCT00392795) (17).

To be included into this nested PTSD cohort study, patients were required to complete **Pre-existing PTSD assessments** (**Figure E1 in the online data supplement**), which were incorporated into the parent cohorts from February 15, 2009 onwards. While the overall prevalence rates and risk factors of PTSD from the BRAIN ICU (civilian patients) study have already been published (13), this cohort is unique and substantially improves on prior reports in three ways: the cohort comprises of veteran patients (MIND-ICU) and civilian patients (BRAIN-ICU) allowing comparisons; the cohort used had an enhanced and rigorous assessment for pre-existing PTSD as described below; and the cohort uses PCL-S threshold and DSM mapping methods to ascertain the incidence of ICU-related PTSD. Informed consent was obtained from patients or their health-care proxy. If consent was initially obtained from a health-care proxy, the patient provided informed consent when deemed competent.

Pre-existing PTSD assessments

Pre-existing PTSD was used as another demographic characteristic for this cohort and potential risk factor for ICU-related PTSD, but did not exclude subjects from this study. Prior to hospital discharge, we screened patients for pre-existing PTSD (**Figure E1 in the online data supplement**). When patients reported a previous history or diagnosis of PTSD, we identified the traumatic event and then confirmed the probability of ongoing sequelae due to that prior traumatic event with the PTSD Checklist-Event Specific Version (PCL-S) (18). We categorized patients with a PCL-S score ≥ 50 as having a high probability of pre-existing PTSD (i.e. PTSD prior to the ICU) (13, 19).

Patients with no prior diagnosis of PTSD were asked about their prior exposure to traumatic stressors using a modified Traumatic Life Event Questionnaire (TLEQ) (20, 21).

Patients who reported one or more traumatic stressors on the modified TLEQ (score ≥ 1) were also evaluated with the PCL-S anchored around the most significant traumatic event; those with PCL-S scores ≥ 50 had high probability of pre-existing PTSD.

PTSD assessments associated with critical illness (ICU-related PTSD)

At 3 and 12 months after hospital discharge, we used the PCL-S anchored to the ICU experience as the traumatic event to evaluate survivors for new PTSD related to their ICU stay (**Figure 1**). We categorized patients as having a high probability of PTSD, using two methods: first a cut-off based threshold approach relying on PCL-S score ≥ 50 and an item mapping approach based on DSM-IV criteria (13, 22).

Statistical analysis

We present continuous data as medians (IQRs) and categorical variables as percentages. To assess the relationships of baseline and in-hospital characteristics with ICU-related PTSD, we used a proportional odds logistic regression model with the PCL-S scores as the continuous outcome for each time point. The following risk factors were included: age at enrollment, sex, pre-existing PTSD, pre-existing depression, IQCODE (short Informant Questionnaire on Cognitive Decline in the Elderly) score, mean daily modified SOFA (Sequential Organ Failure Assessment) score, delirium duration, mean daily dose of benzodiazepines in the ICU, mean daily dose of opiates in the ICU, and veteran status. To minimize bias in multivariable models due to missingness in covariates or outcomes, we included in our main analysis all patients who survived and remained in the study at each time point, using multiple imputation to account for missing data (23). Imputation of ICU-related PCL-S scores was required in 31 of 212 (15%) subjects at 3 months and in 27 of 187 (14%) subjects at 12 months. We used R version 3.1.2 for all analyses. We used the lrm function from the rms package (version 3.14-6) for proportional

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odds logistic regression, in conjunction with the aregImpute and fit.mult.impute functions from the Hmisc package (0.9-5) for multiple imputation.

RESULTS

ICU Cohort Enrollment

We enrolled 255 survivors of critical illness in this study, including 72 veteran patients and 183 civilian patients, between February 15, 2009 and March 27, 2010 (**Table 1**). Between enrollment and 3-month follow-up, 29 patients (11%) died and 14 (5%) withdrew from the study, leaving 212 patients eligible for the 3-month ICU-related PTSD assessments. Between 3- and 12-month follow-ups, an additional 23 subjects (11% of 3-month survivors) died and 2 (1%) withdrew, leaving 187 patients eligible for the 12-month ICU-related PTSD assessments. The sixteen patients who withdrew were similar to those who did not withdraw with respect to demographics (e.g., age, sex, severity of disease, length of ICU stay, history of depression).

Baseline ICU Cohort Characteristics

Among the 212 survivors eligible for follow-up, the veteran and civilian group characteristics differed slightly, as shown in **Table 2**. Compared with civilian participants, veterans tended to be older but had lower severity of illness. Delirium was common in both groups but slightly less common among veterans. Among those with delirium, the median duration of delirium was 3 (1-6) days. Pre-existing PTSD history or trauma exposure information was obtained from 178 (84%) of the 212 survivors; 21 (12%) of these self-reported a pre-existing PTSD diagnosis, 149 patients had a TLEQ score ≥ 1, and 8 had no traumatic life events per the TLEQ. Among the 170 patients with a history of PTSD or traumatic exposure (TLEQ score ≥ 1), 168 completed the PCL-S, and 17 (10%; 7 veterans, 10 civilians) met criteria for high probability

of pre-existing PTSD based on a PCL-S score ≥ 50. No patient with pre-existing PTSD identified warfare or life-threatening illness as his or her main prior traumatic event. No patient who withdrew met criteria for high probability of pre-existing PTSD.

ICU-related PTSD Incidence and Symptom Clusters

Of the 212 patients that were alive and still in the study at 3-month follow-up, 181 completed the ICU-related PTSD assessment, with a median PCL-S score of 22 (19-28); the median scores were 23 (20-28) among veterans and 21 (19-27) among the civilian patients (**Table 3, Figure 2**). Similarly, among 187 that were alive and still in the study at 12 months, 160 completed ICU-related PTSD assessment, with a median PCL-S score of 22 (18-28); median scores were 20 (17-28) among veterans and 23 (18-27) among the civilian patients (**Table 3, Figure 2**). In general, 1-8% had a high probability of ICU-related PTSD, whether assessed by PCL-S score or DSM-IV mapping, at either follow-up time points (**Table 3**). Of the 194 subjects assessed at 3 and/or 12 months, the cumulative incidence of ICU-related PTSD over 12 months was 6% (11 of 194) based on PTSD Checklist-Event Specific Version scores ≥ 50, and 12% (23 of 194) based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) PTSD criteria. PTSD symptom clusters of avoidance and hyperarousal were observed in 40% of our patients at both time points (**Table 3**).

Risk Factors for ICU-related PTSD

After adjusting for covariates, at both 3 and 12 months, pre-existing PTSD was independently associated with higher odds of greater PCL-S scores (3-month odds ratio [OR], 7.7 [95% CI 2.5-23.5, $P < 0.001$]; 12-month OR, 10.7 [95% CI 3.3-35.1, $P < 0.001$]), as was pre-existing depression (3-month OR, 2.8 [95% CI, 1.6-5.1, $P < 0.001$]; 12-month OR, 2.0 [95% CI, 1.1-3.7, $P = 0.03$]); see **Figure 3**. Delirium duration was not significantly associated with greater

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PCL-S scores at either 3 or 12 months. Though being a veteran ICU survivor was a risk factor for ICU-related PTSD at 3 months (OR, 2.6 [95% CI, 1.2-5.7, $P = 0.01$]), it was not a risk factor at 12 months after accounting for other confounders (OR, 1.3 [95% CI, 0.6-2.8, $P = 0.48$]) (**Figure 3**).

DISCUSSION

Our investigation was the first ever to rely on validated methods to identify ICU-related PTSD incidence in a multicenter, prospective, observational cohort study of veteran and civilian survivors of critical illness. We demonstrated that the cumulative incidence of PTSD associated with the ICU experience was 6-12% in the year after hospital discharge and that approximately two in five ICU survivors developed clinically significant PTSD symptoms of avoidance or hyperarousal, which both occurred twice as frequently as intrusion symptoms. This study found pre-existing PTSD and depression were both strongly associated with ICU-related PTSD, while no association was detected between PTSD risk and duration of delirium, opiate dose, or benzodiazepine dose. Veterans were not consistently at a higher risk of developing ICU-related PTSD.

A major strength of this study was our multicenter cohort design that included both veteran and civilian participants from mixed medical and surgical ICU populations. Additionally, we used a rigorous approach to identify pre-existing PTSD. First, we asked patients about a prior diagnosis of PTSD. Second, in patients that did not carry a formal diagnosis, we evaluated them for exposure to traumatic events and assessed which of those experiences were most stressful. Third, we further tested those with a prior diagnosis of PTSD or exposure to traumatic life events with the PCL-S anchored to the greatest prior traumatic event to ascertain whether they had a

high probability of pre-existing PTSD. Even though some patients had a life threatening illness in the past, none of the patients with pre-existing PTSD identified critical illness as their stressor. This enabled us to determine the incidence of ICU-related PTSD, which we accomplished using two methods: the established cutoff approach to the PCL-S and DSM-IV mapping of PTSD criteria.

Our results demonstrate the cumulative incidence of ICU-related PTSD risk at one-year to be in the 10% range, which is similar to some previously published prevalence rates (4, 13, 24) and incidence rate (4, 5), and extends those findings to include veterans who survive a critical illness. In contrast, our observed incidence rates of PTSD risk at 3 and 12 months are lower than those of other reported prevalence rates of up to 64% (9-11). Many of these prior studies utilized brief screening questionnaires or clinician diagnosis (10), sought to identify PTSD without attempting to anchor it explicitly to critical illness, and did not use DSM-IV mapping of PTSD symptoms. Our study is similar in size to the largest post-ICU PTSD studies that have demonstrated a similar point prevalence of 8-9% and incidence of 9-13% based on follow-up times of 3 months or less (4, 5, 24). Other post-ICU PTSD studies with a follow-up time of at least 12 months have reported wider prevalence ranges but included fewer than 100 subjects (25-31). No study has used detailed self-report assessments for prior PTSD among enrolled veterans; thus our study is the first to report PTSD incidence related to the ICU experience in a cohort of both veteran and civilian patients. To put our results in perspective, the definitive National Comorbidity Survey Replication used DSM-IV criteria to determine the 12-month prevalence of PTSD among the general US adult population and found that only 3.5% had PTSD (32), which is about one-third of our cumulative incidence rate in patients 12 months after

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a critical illness. Thus, despite lower rates of PTSD related to critical illness in our cohort, the rates we observed are still significantly greater than the population at large.

Although the PTSD symptom clusters of intrusion and avoidance have been found in survivors up to one year after critical illness, these have been quantified using elements of the Impact of Event Scale and Davidson Trauma Scale in small populations with limited follow-up rather than using DSM-IV criteria (11, 33). In our combined veteran and civilian cohort, we mapped each of the three PTSD symptom clusters based on DSM-IV criteria and only considered a symptom positive if a patient had a score on any of the corresponding questions of ≥ 3, which reflects clinically significant impairments. Almost half of our patients had hyperarousal and avoidance symptoms, with a lower but substantial proportion of 20% exhibiting intrusion symptoms. While we did not explore these intrusive symptoms, these repeatedly experienced memories in ICU survivors have been reported to be hallucinatory or delusional (i.e., consistent with ICU psychosis) rather than reality-based and linked to classic PTSD (34). A weakness of our symptom cluster determination is its basis on a three-factor DSM-IV based model; we did not examine four- or five-factor PTSD models that incorporate the dimensions of dysphoria and anxious arousal (35).

In contrast to older studies (24, 36, 37) but in line with recent studies (11), we found that benzodiazepine dose had no association with ICU-related PTSD after adjusting for severity of illness, pre-existing depression, pre-existing PTSD, and other risk factors. Although over 65% of our ICU patients received a benzodiazepine, the total exposure by dose was small (6.3 mg median 24h dose) and may have resulted in a lack of variance. There have been additional pharmacologic associations with exogenous hydrocortisone (38), the hypothalamic-pituitary-adrenal axis (39), and lower PTSD rates, but we did not quantify this medication class or the

associated genetic polymorphisms in our study (40). In concordance with prior work, systematic reviews, and meta-analyses (6, 10-12), we found that sex and severity of illness did not influence outcomes, whereas a history of depression was strongly associated with ICU-related PTSD. Aligning with our group's prior work (13, 36) with another well-done long-term study of acute lung injury survivors (31), delirium duration did not affect ICU-related PTSD in this mixed cohort composed of veterans and civilians.

Patients, families, co-workers, outpatient mental health practitioners, and primary care providers should be vigilant about the possibility of PTSD and the prominent constellation of avoidance and hyperarousal symptoms after critical illness. We want the readership to be clear that these ICU-related PTSD symptom clusters are truly problematic signs and not measurement artifact, although they represent a forme fruste of PTSD, rather than full-blown PTSD. As compared with other PTSD symptoms, avoidance is associated with functional impairment and disability after a medical illness, as patients often ignore significant subsequent health demands given they are reminders of the inciting medical event. For example, PTSD anchored to an initial myocardial infarction results in non-adherence to cardiac medications (41). PTSD treatment strategies targeting avoidance symptoms, such as prolonged exposure and eye movement desensitization and reprocessing, may need to be considered for the ICU survivor (42). For those patients with PTSD-related hyperarousal, pharmacologic antidepressants targeting norepinephrine reuptake inhibition may induce anxiolysis, calm the sympathetic nervous system, and limit future cardiovascular consequences (43). It is possible that antipsychotics, particularly of the atypical classes, may decrease rates of intrusion (44). Although PTSD may not represent a very frequent psychological consequence after a critical illness, a history of PTSD and

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depression are strong markers for ICU-related PTSD risk, and healthcare providers caring for these patients should be cognizant about the possible presence of this condition.

A similar PTSD prevalence of 8% exists in current and former service members deployed to the Iraq and Afghanistan conflicts, steering the US Department of Defense and VA hospitals to construct numerous screening, diagnosis, treatment, and rehabilitation programs to address this condition (45). The civilian sector, on the other hand, has no coordinated PTSD strategy for the 5 million annual survivors of critical care illness. Currently, the international psychological aftercare for ICU survivors is not organized proactively; rather, it is largely reactive in response to disabling reports from survivors, caregivers, and primary care providers. The Institute of Medicine in the United States has recommended a systematic collection, analysis, and dissemination of data assessing the quality of post-conflict PTSD care in the military and veteran populations (46). We suggest that the same should apply to the large civilian and veteran populations of critically ill survivors.

Our study had many strengths as outlined earlier, but it also has some limitations. One major limitation is that our measurement of pre-existing PTSD during the hospital phase may have been contaminated by current psychological distress and early ICU-related acute stress phenomena. We do not know if our pre-existing PTSD assessments are robust to such post-ICU reporting biases. This study limitation could be partly conquered in future work on elective surgical populations, where pre-existing PTSD could be properly measured before the acute hospitalization and ICU stay. We do note the small number of patient withdrawals uniquely lacked pre-existing PTSD, perhaps speaking to their implicit bias against further follow-up and evaluation for ICU-related PTSD. Another study limitation is that one of our PTSD determinations was DSM-IV based, as study inception occurred prior to the interim two-decade

revision, the DSM-5 (47) that now makes no differentiation between acute and chronic PTSD when symptoms last at least one-month. It is important to note both of our PTSD measurements related to PTSD risk, not PTSD diagnosis (48-50). Furthermore, as is the case with most observational studies, no claims of causality can be made. Finally, though we included as many variables as possible (without overfitting our models) that we believed to have strong scientific evidence as risk factors, it is possible that we did not account for all confounders – for example, PTSD genetic markers (40, 51), veteran deployment classification (52), or ICU steroid usage (38) could have a potentially confounding association with our risk factors and PCL-S scores. Even with our robust follow-up at 3 and 12 months, some patients had missing history and outcomes data. Given that excluding such patients would bias our results, we used multiple imputation to account for missing data in our multivariable modeling per published recommendations (23).

The long-term consequences of ICU-related PTSD symptom clusters and PTSD diagnosis on quality of life, return to work, and societal reintegration remain unclear, as does the neurobiological basis for distinct prevention and treatment strategies in this population (51). Further epidemiologic work on ICU-related PTSD should strive to use the most current, reliable, and validated DSM-5 based screening and diagnostic tools, as well as untangle the intertwined roles of pre-existing psychiatric disorders and post-hospitalization mental health recovery (53). Future ICU-related PTSD work may focus on expanded and novel ICU multidisciplinary interventions, such as ICU diary usage for prevention, pharmacologic prophylaxis for PTSD, psychological treatment, and combined cognitive with physical therapy (46, 54, 55), as well as conducting earlier in-hospital mental health screening and raising awareness of this disease among the individuals caring for ICU survivors.

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INSTITUTIONAL REVIEW BOARD APPROVAL:

The BRAIN-ICU and MIND-ICU studies obtained ethics approval Vanderbilt University Human Research Protection Program (institutional review board numbers 060593 and 040542). Participants and/or legally authorized representatives (i.e. surrogates) gave informed consent before taking part.

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Figure 1. Assessment of ICU-related PTSD

Abbreviations: PTSD, posttraumatic stress disorder; Diagnostic and Statistical Manual of Mental Disorders (DSM)

Figure Legend: At 3 and 12 months after hospital discharge, we used the PTSD Checklist-Event Specific Version (PCL-S) anchored to the ICU experience as the traumatic event to evaluate survivors for new PTSD related to their ICU stay. We categorized patients as having a high probability of PTSD, using two methods: first a cut-off based approach relying on PCL-S score ≥ 50 and an item mapping approach based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria (13, 22).

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Figure 2. ICU-related PTSD (i.e., PTSD symptoms related to the ICU experience) at 3- and 12-month follow-up

Abbreviations: PTSD, posttraumatic stress disorder; PCL-S, PTSD checklist-event specific version; VA, Veteran Affairs

Figure Legend: The box and whisker plots show the PCL-S score related to the ICU experience at 3 months and 12 months, separately for the civilian and veteran populations. The horizontal line within each box indicates the median PCL-S score, the upper and lower limits of the boxes indicate the 25th to 75th interquartile range, the ends of the vertical whiskers indicate 1.5 times the interquartile range, and the black dots indicate values outside these ranges. A score of 50 or higher on the PCL-S denotes high probability of ICU-related PTSD.

Figure 3. Risk factors for ICU-related PTSD at 3 and 12-month follow-up

Abbreviations: PTSD, posttraumatic stress disorder; SOFA, modified Sequential Organ Failure Assessment score excluding the Glasgow Coma Scale score component; IQCODE, short Informant Questionnaire on Cognitive Decline in the Elderly; PCL-S, PTSD checklist-event specific version; *benzodiazepine and opiate doses were cube-root transformed to reduce the influence of extreme outliers

Figure Legend: This forest plot denotes the association between risk factors of interest and the odds of having a higher PCL-S score at 3 and 12 months. For each risk factor, the point estimate and 95% CI are shown. Interpretative example: At both 3 and 12 months, pre-existing PTSD was independently associated with higher odds of greater PCL-S scores (3-month odds ratio [OR], 7.7 [95% CI, 2.5-23.5, $P < 0.001$]; 12-month OR, 10.7 [95% CI, 3.3-35.1, $P < 0.001$]), as compared to a patient without pre-existing PTSD.

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PREVIOUS PRESENTATION OF MATERIAL:

Portions of this work have been presented at the following:

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Southern Society of Clinical Surgery in Nashville, TN, on March 24, 2015

Association for VA Surgeons Annual Meeting in Miami, FL on May 3, 2015

5th Annual American Delirium Society in Baltimore, MD on June 2, 2015

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Table 1. Enrollment and follow-up for PTSD ICU survivor cohort

	Veteran	**Civilian**	**Overall**
Hospital survivors in PTSD cohort	72	183	255
Died between discharge and 3 months	8 (11%)	21 (11%)	29 (11%)
Withdrew between discharge and 3 months	1 (1%)	13 (7%)	14 (5%)
Available for PTSD assessment, 3 months	63 (88%)	149 (81%)	212 (83%)
Died between 3 and 12 months	11 (17%)	12 (8%)	23 (11%)
Withdrew between 3 and 12 months	1 (2%)	1 (1%)	2 (1%)
Available for PTSD assessment, 12 months	51 (81%)	136 (91%)	187 (88%)

Abbreviations: PTSD, posttraumatic stress disorder; Veteran, Veteran Affairs ICU survivors; Civilian, Civilian ICU survivors

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Table 2. Baseline and in-hospital characteristics for PTSD cohort eligible for 3-month follow-up

	Veteran N=63	**Civilian N=149**	**Overall N=212**
Baseline Characteristics			
Age at enrollment, in years	64.6 (61.3-73.7)	56.6 (46.4-65.2)	60.9 (50.0-68.2)
Race, White, n (%)	58 (92%)	128 (86%)	186 (88%)
Sex, Male, n (%)	58 (92%)	78 (52%)	136 (64%)
IQCODE at enrollment	3.06 (3.00-3.19)	3.00 (3.00-3.12)	3.00 (3.00-3.12)
Depression history, n (%)	20 (32%)	58 (39%)	78 (37%)
Charlson comorbidity index	2.0 (1.0-4.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)
ICU type, n (%)			
Medical	48 (76%)	73 (49%)	121 (57%)
Surgical	15 (24%)	76 (51%)	91 (43%)
APACHE II at ICU admission	17.0 (12.5-22.0)	24.0 (17.0-30.0)	21.0 (16.0-27.2)
Pre-existing PTSD	7 (15%)	10 (8%)	17 (10%)
In-hospital characteristics			
Mean ICU modified SOFA	4.3 (3.4-6.0)	5.4 (4.3-7.4)	5.0 (4.0-7.0)
Delirium, n (%)	36 (57%)	110 (74%)	146 (69%)
ICU length of stay	4.4 (2.2-6.9)	4.0 (1.9-10.0)	4.2 (1.9-9.7)
Hospital length of stay	9.1 (6.6-13.2)	9.0 (6.0-17.1)	9.1 (6.0-16.2)
Benzodiazepine exposure, n (%)	35 (56%)	106 (71%)	141 (67%)
Opiates exposure, n (%)	43 (68%)	132 (89%)	175 (83%)

Data are presented as median (interquartile range) unless otherwise noted.

Abbreviations: IQR, Interquartile Range; IQCODE, short Informant Questionnaire on Cognitive Decline in the Elderly; APACHE II, Acute Physiology and Chronic Health Evaluation II; modified SOFA, Sequential Organ Failure Assessment score excluding the Glasgow Coma Scale score component; PTSD, posttraumatic stress disorder

Table 3. ICU-related PTSD Incidence and Symptom Clusters

	3-months after hospitalization	12-months after hospitalization
PCL-S Score, median (IQR)	22 (19-28)	22 (18-28)
ICU-related PTSD Incidence, n (%)		
By PCL-S Score ≥50	10 (6%)	2 (1%)
By DSM-IV Mapping	15 (8%)	10 (6%)
ICU-related PTSD Symptom Clusters, n (%)		
Intrusion	25 (14%)	25 (16%)
Avoidance	78 (43%)	60 (38%)
Hyperarousal	82 (45%)	71 (44%)
No ICU-related PTSD Symptom Clusters, n (%)		
No intrusion, No avoidance, No hyperarousal	69 (38%)	74 (46%)

Abbreviations: IQR, Interquartile Range; PTSD, posttraumatic stress disorder; PCL Score, PTSD checklist-event specific version

At 3 and 12 months after hospitalization, 181 and 160 subjects were assessable, respectively.

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Figure 1. Assessment of ICU-related PTSD

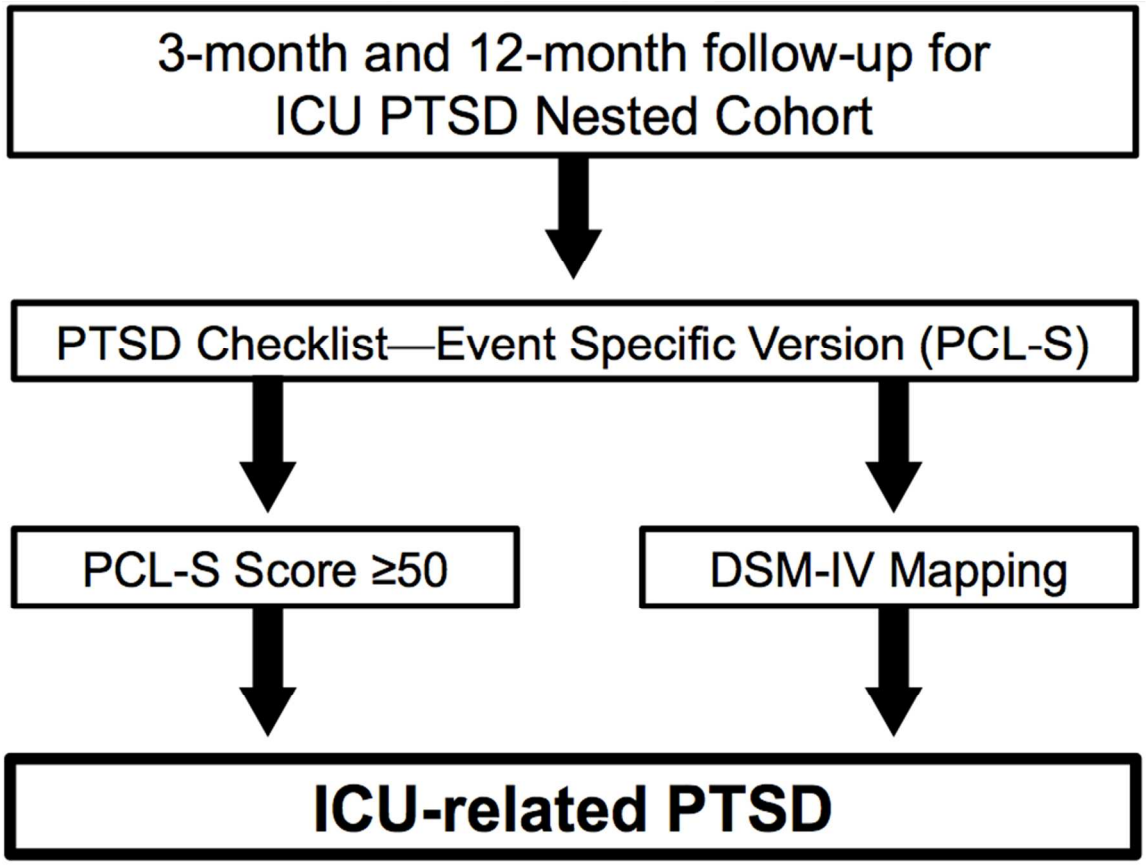

Figure 2. ICU-related PTSD (i.e., PTSD symptoms related to the ICU experience) at 3- and 12-month Follow-up

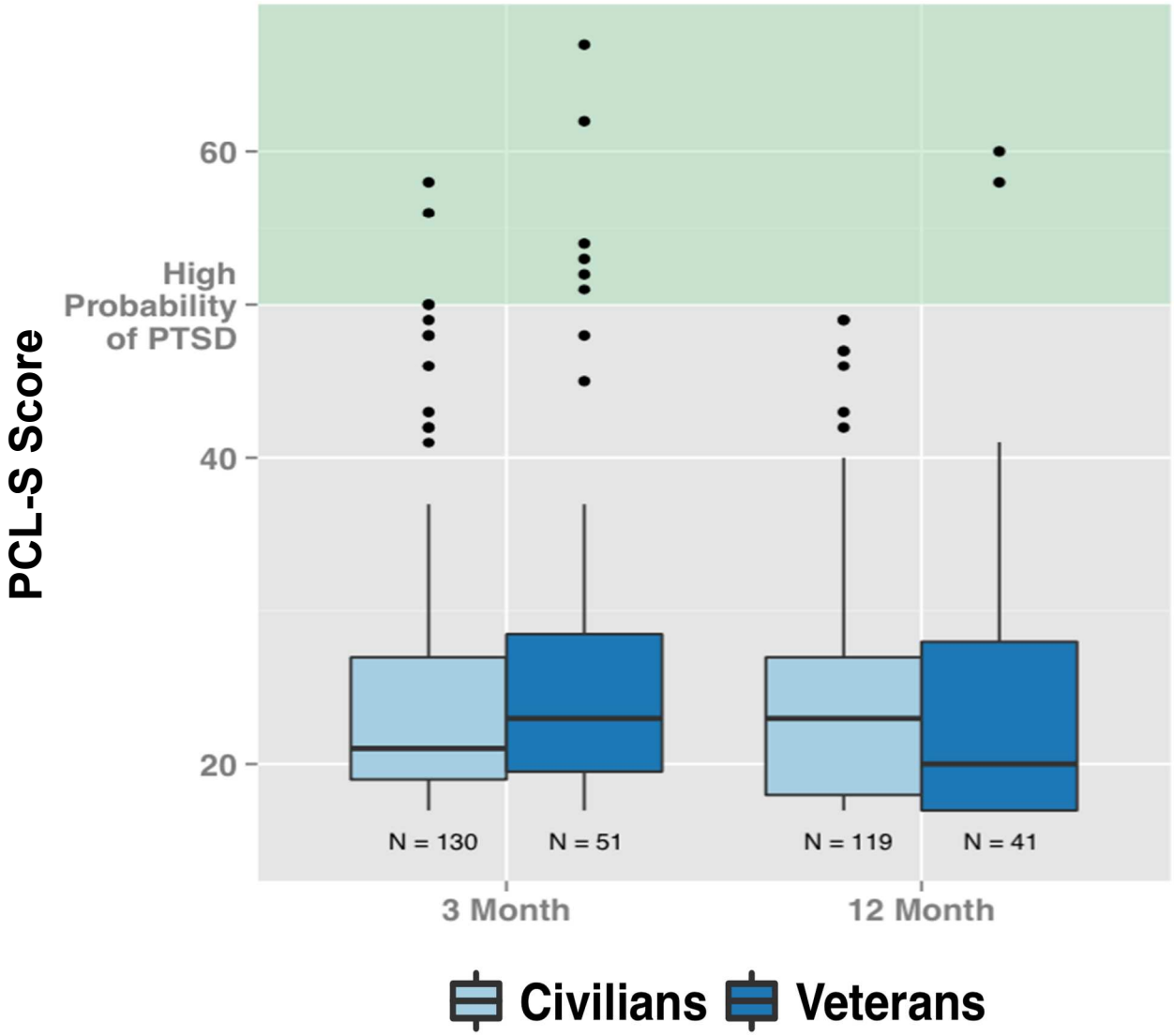

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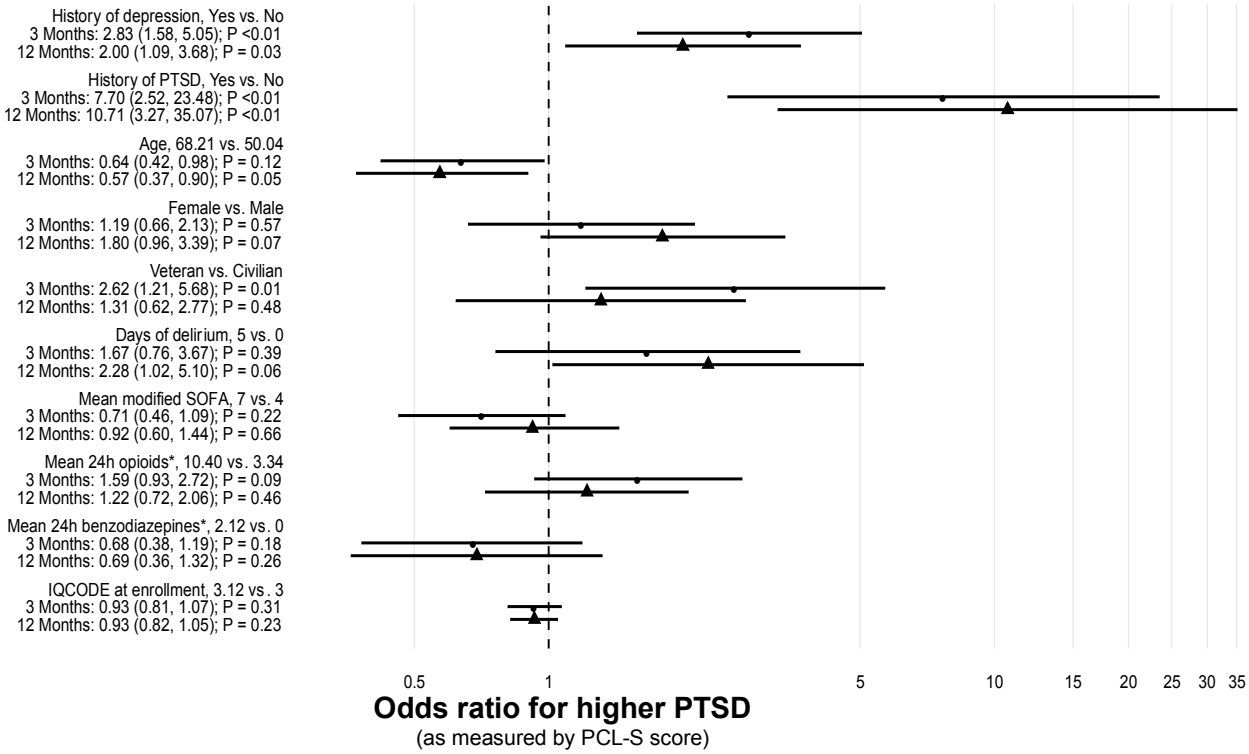
Figure 3. Risk Factors for ICU-related PTSD at 3 and 12-month Follow-up



ONLINE SUPPLEMENT

TITLE:

Incidence and Risk Factors for ICU-related Posttraumatic Stress Disorder In Veterans and Civilians

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METHODS

Study design, population, and patients

This prospective, observational, multicenter cohort study was nested within two observational cohort studies that were conducted in parallel: the Veterans Affairs (VA) patients were enrolled in the Measuring the Incidence and determining risk factors for Neuropsychological Dysfunction in ICU Survivors study (MIND-ICU, ClinicalTrials.gov Identifier: NCT00400062) and the civilian patients were enrolled in the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors study (BRAIN-ICU, ClinicalTrials.gov Identifier: NCT00392795) (E1). The MIND-ICU study enrolled patients in the Nashville VA Medical Center in 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 representing the Veterans Integrated Service Networks (VISN) 9, 19, and 20, respectively. The BRAIN-ICU study (E1) enrolled patients at Vanderbilt University Medical Center (Nashville, TN, USA) and Saint Thomas Hospital (Nashville, TN, USA), though no subjects were included in this PTSD cohort from the latter institution. Institutional review boards at each site approved the study.

The inclusion and exclusion criteria for the parent MIND-ICU and BRAIN-ICU studies were identical and have been previously published along with data regarding long-term cognitive impairment and health related quality of life in the BRAIN-ICU cohort (E1, E2). No data from the MIND-ICU study are published yet. In short, we included adults (aged at least 18 years) with respiratory failure and/or shock, who were admitted to medical or surgical ICUs. We excluded individuals with substantial recent ICU exposure, including those who had been mechanically

ventilated at any time in the 2 months prior to admission, spent more than 5 days in an ICU during the month before admission, or spent more than 72 hours with organ dysfunction during the current ICU admission before screening and enrollment were complete. These previously published exclusions were used to avoid missing early exposure to the ICU environment, arguably when severity was highest. We also excluded patients with significant pre-existing cognitive impairment (identified using the short Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE] (E3). Since the IQCODE was not validated in patients <65 year of age, we first interviewed surrogates and only proceeded with the IQCODE in patients who had memory problems prior to ICU admission. We further excluded those at high risk for pre-existing cognitive deficits owing to neurodegenerative disease, cardiac surgery within the past 3 months, or suspected anoxic injury; those who were blind, deaf, or non-English speakers; individuals for whom follow-up would be difficult because of substance abuse, psychosis, homelessness, or residence at least 200 miles from a study site; those unlikely to survive 24 hours (assessed by a review of medical records or consultation with the medical team); and those for whom informed consent could not be obtained. Informed consent was obtained from patients or their health-care proxy. If consent was initially obtained from a health-care proxy, the patient provided informed consent when deemed competent.

To be included into this nested PTSD cohort study, patients were required to complete **Pre-existing PTSD assessments** (**Figure E1 in the online data supplement**), which were incorporated into the parent cohorts February 15, 2009 onwards. While the overall prevalence rates and risk factors of PTSD from the BRAIN ICU (civilian patients) study have already been published (E2), this cohort is unique and substantially improves on prior reports in three ways: the cohort comprises of veteran patients (MIND-ICU) and civilian patients (BRAIN-ICU)

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allowing comparisons; the cohort used had an enhanced and rigorous assessment for pre-existing PTSD as described below; and the cohort uses PCL-S threshold and DSM mapping methods to ascertain the incidence of ICU-related PTSD.

Baseline characteristics

Enrolled patients were followed daily for up to 30 days, or until death or discharge from the hospital, whichever occurred first. At enrollment we collected demographic and baseline information including age, education level, pre-existing cognitive impairment (short IQCODE) (E3), and history of mental illness, including self-report of depression. We then followed patients during their ICU and hospital stay, collecting data (laboratory and hemodynamic variables) pertaining to severity of illness via the modified Sequential Organ Failure Assessment (SOFA) (E4) score (excluding the Glasgow Coma Scale score component), daily dose of ICU benzodiazepine exposure (expressed in midazolam equivalents), and ICU opioid exposure (expressed in fentanyl equivalents). We assessed patients' mental status twice daily in the ICU and once per day in the wards, evaluating them first for level of consciousness with the Richmond Agitation-Sedation Scale (RASS) (E5) and then for delirium with the Confusion Assessment Method for the ICU (CAM-ICU) (E6) if they were responsive to voice. Patients were deemed delirious if they were responsive to verbal stimuli (RASS score of –3 or higher) and CAM-ICU positive. Patients were defined as comatose if they were unresponsive to verbal stimuli (RASS score of –4 or –5). We calculated duration of delirium as the number of days a patient was CAM-ICU positive during the 30-day study period.

Pre-existing PTSD assessments

Pre-existing PTSD was used as another demographic characteristic for this cohort and potential risk factor for ICU-related PTSD, but did not exclude subjects from this study. Prior to hospital discharge, we screened patients for pre-existing PTSD using a structured approach (**Figure E1 in the online data supplement**). When patients reported a previous history or diagnosis of PTSD, we identified the traumatic event and then confirmed the probability of ongoing sequelae due to that prior traumatic event with the PTSD Checklist-Event Specific Version (PCL-S) (E7). The PCL is a standardized self-report rating scale for PTSD comprising 17 items that correspond to the symptoms of PTSD described in the DSM-IV. The event-specific version allows screening for PTSD resulting from a specific traumatic event. We categorized patients with a PCL-S score ≥ 50 as having a high probability of pre-existing PTSD (i.e. prior to their ICU stay), consistent with published literature (E2, E8, E9).

Patients with no prior diagnosis of PTSD were asked about their prior exposure to traumatic stressors using a modified Traumatic Life Event Questionnaire (TLEQ) (E10, E11). The modified TLEQ is a 23-item self-report measure of 22 types of potentially traumatic events, including natural disasters, exposure to warfare, robbery involving a weapon, physical abuse, life threatening illness, and being stalked. Patients who reported one or more traumatic stressors on the modified TLEQ (score ≥ 1) were also evaluated with the PCL-S anchored around the most significant traumatic event; those with PCL-S scores ≥ 50 were considered to have high probability of pre-existing PTSD.

PTSD assessments associated with critical illness (ICU-related PTSD)

At 3 and 12 months after hospital discharge, trained neuropsychological personnel used the PCL-S anchored to the ICU experience as a traumatic stressor to evaluate survivors for new

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PTSD related to their ICU stay (**Figure 1**). We categorized patients as having a high probability of PTSD, using two methods: first a cut-off based approach relying on PCL-S score ≥ 50 and an item mapping approach based on DSM-IV criteria (E2, E12). Specifically, the 17 questions or symptoms evaluated by the PCL-S are scored from 1 to 5, where 1 indicates that the patient was not at all affected by that symptom and 5 indicates that the patient is extremely affected. A score of ≥ 3 on a question denoted the presence of at least moderately significant symptoms. Questions 1–5 on the PCL-S map onto criterion B of the DSM-IV definition of PTSD (intrusion symptoms); questions 6–12 map onto criterion C (avoidance symptoms); questions 13–17 map onto criterion D (hyperarousal symptoms). All patients in this cohort had a life-threatening critical illness and met criterion A (exposure to a traumatic event). In keeping with DSM-IV criteria, patients were considered to have high probability of PTSD if they had at least one positive intrusion symptom, at least three positive avoidance symptoms, and at least two positive hyperarousal symptoms.

Statistical analysis

We present continuous data as medians (IQRs) and categorical variables as percentages. To assess the relationships of baseline and in-hospital characteristics with ICU-related PTSD, we used two separate regression models with the PCL-S scores at each time point (3 and 12 months after hospital discharge) for the continuous outcome. Because of the skewed distribution of the PCL-S scores, the assumption of normal error terms for linear regression was not met; therefore we used proportional odds logistic regression, which does not assume a specific distribution. The proportional odds assumption was met in that the curves on the various cumulative logits are parallel. Since the score test associated with the proportional odds test is known to be liberal and

could possibly lead to inappropriate rejection of the proportional odds assumption (E13), the assumptions were evaluated graphically, using both adjusted and unadjusted methods (E14).

The following risk factors—which we selected *a priori* based on previous research and biological plausibility—were included in the models: age at enrollment, sex, pre-existing PTSD, pre-existing depression, IQCODE score, mean daily modified SOFA score, delirium duration, mean daily dose of benzodiazepines in the ICU, mean daily dose of opiates in the ICU, and veteran status (veteran versus civilian). In the models, benzodiazepine and opiate doses were cube-root transformed to reduce the influence of extreme outliers; age, delirium duration, and mean modified SOFA were modeled with the use of restricted cubic splines to allow for nonlinear associations. Our final model had 13 degrees of freedom; given our sample size (187 patients at 12-month follow-up), we could reliably fit a model with 15 degrees of freedom without major risk of overfitting (E14). For continuous variables, we compared the 75th percentile of our study population to the 25th percentile.

Missing data management

To minimize bias in multivariable models due to missingness in covariates or outcomes, we included in our main analysis all patients who survived and remained in the study at each time point, using multiple imputation to account for missing data (E15-E17). In the multiple imputation, we included all covariates used in the models, as well as other variables that might predict missingness (including additional information on hospital illness, such as days of severe sepsis and mechanical ventilation). Missing data in our models related to prior self-reported history of PTSD at discharge (34 of 212 (16%) patients at 3 months and 31 of 187 (17%) patients at 12 months). Imputation of ICU-related PCL-S scores was required in 31 of 212 (15%) subjects at 3 months and in 27 of 187 (14%) subjects at 12 months. As in previous work (E1, E2), for

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days with no delirium assessments, we used single imputation based on the mental status on days immediately prior to and following any day with no available assessment; in our cohort, this was necessary for only 3.5% of patient days. Patients with missing data at one or both time points tended to be more often from the VA population, slightly older, and have more preexisting cognitive and physical impairment at baseline. They also had more sepsis, delirium and coma in the hospital, had a longer hospital stay and were more often discharged to an LTAC. We included explanatory variables including all model covariates (delirium, age, prior history of PTSD, days of severe sepsis, and cognitive impairment) in addition to other explanatory variables in our imputation algorithm in order to address these issues, assuming that data is missing at random.

We used R version 3.1.2 for all analyses. We used the lrm function from the rms package (version 3.14-6) for proportional odds logistic regression, in conjunction with the aregImpute and fit.mult.impute functions from the Hmisc package (0.9-5) for multiple imputation. We used 8 imputed data sets. These 8 complete data sets were analyzed and the results from all 8 imputed datasets are pooled for overall inference using Rubin's rules, which account for the uncertainty associated with imputed values. Our results were qualitatively similar whether looking at multiply imputed versus complete case analyses; there were no differences in statistically significant associations between the two sets of models (E18).

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Figure E1. Study eligibility and assessment of pre-existing PTSD for ICU-related PTSD cohort

Abbreviations: PTSD, posttraumatic stress disorder; BRAIN-ICU, Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors study (Civilian ICU survivors); MIND-ICU, Measuring the Incidence and determining risk factors for Neuropsychological Dysfunction in ICU Survivors study (Veterans Affairs ICU survivors)

Figure Legend: This prospective, observational, multicenter cohort study was nested within two parent studies with identical eligibility criteria (e.g., inclusion of those with respiratory failure and/or shock). Veteran patients were enrolled in the MIND-ICU study and civilian patients were enrolled in the BRAIN-ICU study. To be included into this nested PTSD cohort study, patients were required to complete pre-existing PTSD assessments, which were incorporated into the parent cohorts from February 15, 2009 onwards. Patients were asked about a prior diagnosis of PTSD. In patients that did not carry a formal diagnosis, we evaluated them for exposure to prior traumatic life stressors using a modified Traumatic Life Event Questionnaire (TLEQ). Patients with a prior diagnosis of PTSD or a TLEQ score ≥ 1 then underwent testing with the PTSD Checklist-Event Specific Version (PCL-S) anchored to the most severe prior traumatic event to ascertain whether they had a high probability of pre-existing PTSD (PCL-S score ≥ 50). PTSD assessments associated with critical illness (i.e., ICU-related PTSD) were then performed at 3 and 12 months after hospital discharge (also see **Figure 1**).

Figure E1. Study eligibility and assessment of pre-existing PTSD for ICU-related PTSD cohort