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## Delirium, Depression and Long-Term Cognition

Patricia S. Andrews, MD<sup>1,2,3</sup>, Jennifer Thompson, MPH<sup>4</sup>, Rameela Raman, PhD<sup>2,4,5</sup>, Chelsea Rick, DO<sup>6</sup>, Amy Kiehl, MA<sup>2,7</sup>, Pratik Pandharipande, MD MSCI<sup>2,5,8</sup>, James C. Jackson, PsyD<sup>2,7,9</sup>, Warren D. Taylor, MD MHSc<sup>1,3,9</sup>, E. Wesley Ely, MD MPH<sup>2,5,7,9</sup>, Jo Ellen Wilson, MD MPH PhDc<sup>1,2,9</sup>

<sup>1</sup>Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN

<sup>2</sup>Critical Illness, Brain Dysfunction, and Survivorship Center, Vanderbilt University Medical Center, Nashville, TN

<sup>3</sup>Center for Cognitive Medicine, Vanderbilt University Medical Center, Nashville, TN

<sup>4</sup>Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN

<sup>5</sup>Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN

<sup>6</sup>Department of Medicine, Division of Geriatric Medicine, Vanderbilt University Medical Center, Nashville, TN

<sup>7</sup>Department of Medicine, Division of Pulmonary and Critical Care, Vanderbilt University Medical Center, Nashville, TN

<sup>8</sup>Department of Anesthesiology, Division of Anesthesiology Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN

<sup>9</sup>Veteran's Affairs TN Valley, Geriatrics Research, Education and Clinical Center, Nashville, TN

### Abstract

**Objectives:** We examined whether pre-admission history of depression is associated with less delirium/coma free (DCF) days, worse one-year depression severity and cognitive impairment.

**Design and Measurements:** A health proxy reported history of depression. Separate models examined the effect of pre-admission history of depression on: a) ICU course, measured as DCF days; b) depression symptom severity at 3 and 12 months, measured by the Beck Depression Inventory II (BDI-II); and c) cognitive performance at 3 and 12 months, measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) global score.

**Setting and Participants:** Patients admitted to the medical/surgical ICU services were eligible.

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**Corresponding author:** Patricia S. Andrews, MD, The Vanderbilt Psychiatric Hospital, 1601 23rd Avenue South, Nashville, TN 37212, Phone: (615) 936-3555, Fax: (615) 875-0686, patricia.andrews@vumc.org.

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**Results:** Of 821 subjects eligible at enrollment, 261 (33%) had pre-admission history of depression. After adjusting for covariates, pre-admission history of depression was not associated with less DCF days (OR 0.78, 95% CI, 0.59 – 1.03 p = 0.077). A prior history of depression was associated with higher BDI-II scores at 3 and 12 months (3 months OR 2.15, 95% CI, 1.42 – 3.24 p = <0.001; 12 months OR 1.89, 95% CI, 1.24 – 2.87 p = 0.003). We did not observe an association between pre-admission history of depression and cognitive performance at either 3 or 12 months (3 months beta coefficient –0.04, 95% CI, –2.70 – 2.62 p = 0.97; 12 months 1.5, 95% CI, –1.26 – 4.26 p = 0.28).

**Conclusion:** Patients with a depression history prior to ICU stay exhibit a greater severity of depressive symptoms in the year after hospitalization.

### Keywords

delirium; depression; cognitive impairment

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### Introduction

Over the last decade, we have seen an increase in survival rates from critical care stays. However, critical care survivors are at increased risk for long-term physical, psychological, and cognitive impairments.(Needham et al., 2012) This constellation of symptoms is collectively known as post-intensive-care syndrome (PICS).(Needham et al., 2012) The Society of Critical Care Medicine has identified PICS as an area in need of further research to improve the outcomes of critical care survivors.(Needham et al., 2012) While many researchers have studied how premorbid medical and demographic factors influence adverse long-term outcomes, relatively few have examined how pre-existing psychiatric illnesses such as depression may influence intensive care unit (ICU) course and post-ICU outcomes.

Delirium is a key negative prognostic indicator of poor post-ICU course. It is a clinical syndrome characterized by acute fluctuations in attention and cognition with a prevalence ranging from 60–87% in the ICU.(Ely et al., 2001; Sakuramoto et al., 2015) Individuals who develop delirium in the hospital have an increased risk for complications, longer length of stay and increased likelihood for discharge to a nursing facility.(Gleason et al., 2015) Multiple pre-morbid chronic conditions increase the risk for delirium, most notably dementia and frailty. Depression prior to coronary artery bypass graft surgery has been identified as a risk factor as well.(Greaves et al., 2020; Oldham et al., 2019)

Delirium in the ICU is also associated with negative long-term post-discharge outcomes including worsening of cognitive performance, emergence of mental health disorders, and disability. Delirium is a risk factor for cognitive impairment and can also accelerate cognitive decline.(Davis et al., 2012; Goldberg et al., 2020) Longer delirium duration is also associated with greater disability in the following year.(Brummel et al., 2014) Along with changes in cognitive performance, the most frequent psychological sequela found in ICU survivors is depression. Depression affects approximately one third of adults in the ICU and increases the risk of mortality in the 2 years after discharge.(Hatch et al., 2018; Davydow et al., 2009; Wang et al., 2018; Rabiee et al., 2016)

It is unclear how depression and cognitive performance deficits may interact in PICS. In adult and geriatric populations depression is itself a risk factor for cognitive impairment. (Barnes et al., 2006) The Framingham heart study that followed patients over 17 years found that depressed participants had more than a 50% increased risk for dementia. (Saczynski et al., 2010; Pandharipande et al., 2014). A meta-analysis of 23 studies found that late-life depression was associated with a significant risk for vascular and Alzheimer's dementia. (Diniz et al., 2013) Cognitive deficits in attention, memory and executive function are frequently observed in both depressed patients and ICU survivors who suffered delirium. (Murrrough et al., 2011; Pandharipande et al., 2014)

The purpose of the study was to examine whether a pre-admission history of depression is associated with acute and long-term critical care outcomes. We hypothesized that a pre-admission history of depression would be associated with a more complicated ICU course, quantified as days of delirium or coma. We also hypothesized that pre-admission history of depression would be associated with greater levels of cognitive impairment and greater depression severity in the year following ICU discharge.

## Methods

### Study population and setting

Adults admitted between March 2007 and May 2010 with respiratory failure, cardiogenic shock, or septic shock to the medical/surgical ICU services at Vanderbilt University Medical Center and Saint Thomas Hospital in Nashville, Tennessee, were eligible for enrollment in the BRAIN-ICU longitudinal cohort study. We excluded patients with significant recent ICU exposure, defined as anyone who: a) had mechanical ventilation at any point 2 months before the current ICU admission; b) spent 5 days or more in an ICU during the month before the current admission; or c) spent 72 hours or more with organ dysfunction in the current ICU admission. We also excluded individuals for cardiac surgery within the past 3 months, suspected anoxic brain injury, blindness or deafness, non-English speakers, current substance use or psychosis, patients for whom follow-up would be difficult (homelessness, residence > 200 miles from Nashville), patients unlikely to survive 24 hours, and those for whom informed consent could not be obtained. Participants were also excluded due to significant preexisting cognitive impairment, either by a prior neurodegenerative disease diagnosis or due to cognitive impairment identified by an informant, using the Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and the Clinical Dementia Rating (CDR) Scale. Individuals with a score of 3.3 or more on the IQCODE (scale from 1.0 to 5.0 where 5.0 indicates severe cognitive impairment) were assessed by certified evaluators with the CDR scale (scores range from 0 to 3.0, higher scores indicating more severe dementia). Patients with a CDR score of 2.0 or higher (moderate dementia) were excluded.

Informed consent was initially obtained by proxy and later by the patient if the patient regained capacity to consent. All study procedures were reviewed and approved by the local Institutional Review Boards. Details of the BRAIN-ICU study have been reported previously. (Pandharipande et al., 2013)

## Outcomes and covariates

We determined a pre-admission history of depression from the health proxy inquiring if the patient had ever been formally diagnosed with depression or other psychiatric conditions by a healthcare professional. Other baseline characteristics included age, education, illness severity using the Acute Physiology Score of Acute Physiology and Chronic Health Evaluation (APACHE APS) score, comorbidities using the Charlson Comorbidity Index and admission diagnoses. Information on possible pre-hospitalization cognitive impairment using the IQCODE was also obtained from the health proxy.

Patients were evaluated for delirium in the hospital for up to 30 days twice daily in the ICU and daily in the wards. We assessed for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) and level of consciousness using the Richmond Agitation-Sedation Scale (RASS). Patients were positive for delirium if CAM-ICU positive and not comatose (RASS score greater than -3). Throughout the study data was collected on severe sepsis, vital signs and ongoing organ dysfunction using the Sequential Organ Failure Assessment Score (SOFA).

Patients were assessed after hospital discharge at 3 and 12 months (+/- 1 month) by a neuropsychologist or a masters level professional. At these visits depression was assessed using the Beck Depression Inventory-II (BDI-II). Patients were also assessed for PTSD; those results are presented elsewhere.(Jackson et al., 2014)

## Statistical Analysis

In all long-term models, we included patients who had any assessment data available at a given time point (even if the outcome of interest is missing). Missing outcome and covariate data were handled using model-based imputation. All continuous covariates were allowed to have a nonlinear relationship with all the outcomes in all the models using restricted cubic splines, except for IQCODE which had too little variability to allow splines. All analyses were done in R (<https://www.R-project.org/>) and Stata version 15 (<https://www.stata.com/>).

Primary models examined the effect of pre-admission history of depression on: a) ICU course, measured as delirium/coma free days; b) post-discharge cognitive performance, measured by the RBANS global score; and c) post-discharge depression symptom severity, measured by the BDI-II. To examine the effect of depression history on delirium/coma free days we used a proportional odds logistic regression model.

To examine the association of pre-admission history of depression with long-term cognition we used linear regression with history of depression as our primary exposure of interest and RBANS global cognition scores as outcomes. To examine the association of pre-admission history of depression with depression severity we used logistic regression with history of depression as our primary exposure of interest and BDI-II depression scores as outcomes. We created separate models to examine these outcome measures at 3 and 12 months after hospital discharge. All models were adjusted for age, gender, Charlson Score, Framingham Stroke Risk Profile, IQCODE and years of education. Models examining the effect of depression history on delirium/coma free days were also adjusted for AHRQ socioeconomic status index, CSHA frailty and APACHE APS at enrollment.(Bonito AJBC, 2008) Models

examining BDI-II and RBANS also included Apolipoprotein E genotype, mean modified SOFA score in the ICU (“modified” = GCS is not included), days of delirium in the hospital, days of coma in the hospital, days of severe sepsis in the ICU and intervals where O<sub>2</sub> saturations < 90% in the ICU.

## RESULTS

A total of 826 patients were enrolled in BRAIN-ICU between March 2007 and May 2010. Five participants withdrew from all participation. At the 3-month follow up 252 patients died; and 448 of the 569 surviving patients underwent testing. Another 59 patients of the original cohort died before the 12-month follow-up. Of the 510 surviving patients 382 were tested 12 months after discharge (flow diagram previously published). The median age at enrollment was 61 years (IQR: 51-71 years); 261 (33%) had a history of depression prior to their critical illness and 51 (6%) had cognitive impairment at baseline (Table 1). In the long-term follow-up, at the 3-month follow-up 409 patients completed the BDI-II and 375 the RBANS. At 12 months 347 patients completed the BDI-II and 325 the RBANS. After adjusting for demographic and other relevant confounders, pre-admission history of depression, as ascertained by a surrogate questionnaire, was not associated with more delirium/coma free days in the ICU (OR 0.78, 95% CI, 0.59 - 1.03 p = 0.077).

We then examined the association of pre-admission history of depression with long-term cognitive performance measured at 3 and 12 months after hospital discharge. Cognitive performance was measured using the RBANS global cognitive score. We did not observe an effect of pre-admission history of depression on RBANS scores at either 3 months or 12 months (3 months beta coefficient -0.04, 95% CI, -2.70 - 2.62 p = 0.97; 12 months 1.5, 95% CI, -1.26 - 4.26 p = 0.28) (Table 2).

Finally, we examined whether a pre-admission history of depression was associated with depressive symptom severity as measured by BDI-II at 3 and 12 months post-discharge. Patients with a prior history of depression were more likely to have higher BDI-II scores at 3 months and 12 months (3 months OR 2.15, 95% CI, 1.42 - 3.24 p = 0.001; 12 months OR 1.89, 95% CI, 1.24-2.87 p = 0.003).

## DISCUSSION

Our primary finding is that patients with a history of depression prior to ICU stay exhibit a greater severity of depressive symptoms in the following year. A past history of depression was not associated with differences in the number of delirium/coma free days in the ICU. Moreover, past history of depression was not associated with worse cognitive performance over the following year.

Depression is common following ICU stay. Nearly a third of ICU survivors have depression up to 24 months follow-up.(Wang et al., 2017; Bienvenu et al., 2015) We now report that a premorbid history of depression increases this risk for greater post-ICU depressive symptoms over the next year. Although the mean BDI-II scores observed in this cohort at 3 and 12 month follow-up are in the minimal to mild depression severity range, there is a tendency for patients with a prior history of depression to experience more symptoms in the

year following an ICU stay. This relationship may not be unexpected, as life stressors are commonly associated with the development of depression. The events leading to the ICU stay and the ICU stay itself are typically quite stressful. Moreover, any associated disability or recovery period may increase life stress after discharge, potentially through emotional responses to disability, financial or employment stress. We propose that a pre-existing vulnerability to depression, characterized by having had previous episodes, increases the likelihood that such stressors may precipitate the development or worsening of depressive symptoms. In some individuals, this may progress to a full depressive episode.

Premorbid depression was not associated with delirium or coma free days during hospitalization or cognitive outcomes following ICU stay. This finding is consistent with the Oldham et al. study reporting that preoperative depression but not lifetime depression was associated with increased risk of delirium. (Oldham et al., 2019) Unfortunately, while we could identify a premorbid history of depression, we could not determine whether clinically significant depressive symptoms existing immediately prior to ICU admission affected course.

We also did not observe an effect of prior depression on cognition, measured by RBANS scores at 3 months and 12 months. Future studies should explore if the severity of depressive symptoms does associate to worse cognitive performance in this population. Prior studies report that severity of depression is associated with poorer cognitive performance. (Lawrence et al., 2013) It has also been reported that cognitive deficits are still present in patients with remitted depression. (Albert et al., 2018) Thus while premorbid depression is not associated with post-ICU cognitive performance, post-ICU depression is associated with poorer post-ICU performance. Nordness et al. demonstrated that depression at 3 months after hospital discharge was associated with poorer cognition at 3 months and worse executive functioning at 3 and 12 months. (Nordness et al., 2021)

Our study has some strengths, including a large longitudinal sample following subjects up to one year after ICU discharge. Limitations include that history of depression was gathered by proxy during the ICU stay and that we did not measure depressive symptoms at the time of enrollment. We also did not capture how far in the past the history of depression was, how many episodes they may have experienced, and whether they were treated with antidepressant medications. Another limitation is that our findings may not generalize to other populations such as those with recurrent ICU admissions, substance use or pre-existing cognitive impairment. These populations may be at higher risk for a range of neurological or psychiatric disturbances in the post-critical care period. Regarding possible biases patients with missing data were different from those with complete outcomes data. We addressed this using model-based imputation.

It is important to identify patients that have a history of depression prior to an ICU stay and to monitor their symptoms after discharge. These individuals are at increased risk of developing depressive symptoms again. Such depressive symptoms may additionally contribute to cognitive dysfunction in ICU survivors. Although identification and treatment of depression is important to improve these patients' quality of life, it is unclear how well patients with PICS respond to antidepressant management and whether such interventions



benefit post-ICU cognitive performance and reduce disability. Future studies should explore possible treatment options for depression and cognitive impairment in the ICU and after discharge.

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**Table 1.**

## Demographics

Variable	Sample as a whole N=821 <sup>‡‡§§</sup>
Age at enrollment (years)	61 (51 – 71)
Caucasians N (%)	740 (90%)
Males N (%)	420 (51%)
Education (years)	12 (12 – 14)
AHRQ SES Index <sup>*</sup>	50 (48 – 53)
Charlson Comorbidity Index at enrollment <sup>‡</sup>	2 (1 – 4)
APACHE APS at enrollment <sup>‡</sup>	21 (15 – 26)
Framingham Stroke Risk Profile at enrollment <sup>§</sup>	9 (6 – 14)
Apo E4 at enrollment <sup>¶</sup>	
E2 / E2	0.5%
E2 / E3	10.1%
E2 / E4	2.4%
E3 / E3	61.1%
E3 / E4	22.6%
E4 / E4	3.3%
IQCODE at enrollment <sup>#</sup>	3 (3 – 3.1)
Clinical Frailty Scale at enrollment <sup>**</sup>	3 (3 – 5)
Delirium during study period	596 (73%)
Days of delirium in the hospital among everyone	1 (0 – 4)
Coma during study period	517 (63%)
Days of coma in the hospital among everyone	3 (2 – 6)
Days of severe sepsis in the ICU among everyone	572 (70%)
Mean modified SOFA score during ICU stay <sup>‡‡</sup>	5 (4 – 7)
Intervals where O2 saturations < 90% during ICU stay	3 (0 – 12)

<sup>\*</sup> Agency for Healthcare Research and Quality Socioeconomic Status Index

<sup>‡</sup> The Charlson Comorbidity Index ranges from 0 to 33; for each increasing level of comorbidity there is a 2.3-fold increase in the 10-year risk of mortality.

<sup>‡</sup> The Acute Physiology and Chronic Health Evaluation (APACHE) rates ICU mortality on a range of 0-71 using a combination of physiological variables and chronic health conditions. The Acute Physiology Score (APS) of the APACHE is a relative value scale applied to 12 physiologic variables used as a severity adjustment to diagnosis-related groups.

<sup>§</sup> The Framingham Stroke Risk Profile integrates the effect of various vascular risk factors to predict the 10-year probability of incident stroke.

<sup>¶</sup> Apolipoprotein E genotype

<sup>#</sup> The Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a scale ranging from 1.0 to 5.0 where 5.0 indicates severe cognitive impairment.

<sup>\*\*</sup> Clinical Frailty Score ranges from 1 to 9 where 1 indicates very fit and 9 terminally ill.

<sup>††</sup> The Sequential Organ Failure Assessment (SOFA) ranges from 0 to 24 with higher scores indicating more severe organ dysfunction. The modified SOFA score excludes the Glasgow Coma Scale since coma was included separately in our models.

<sup>‡‡</sup> History of depression was missing in 38 participants and were not included in this table but included in the analysis using multiple imputation.

<sup>§§</sup> Continuous variables are described as median values and interquartile range. Categorical variables are described using numbers and percentiles.

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**Table 2.**

Association between history of depression and post-discharge global cognitive performance measured by RBANS and depression severity measured with the BDI-II

	<b>RBANS*</b>	<b>BDI-II<sup>†</sup></b>
<b>3 months follow-up N=450</b>	-0.04 (-2.70, 2.62)	2.15 (1.42, 3.24)
<b>12 months follow-up N=384</b>	1.50 (-1.26, 4.26)	1.89 (1.24, 2.87)

\* Data presented for RBANS as beta coefficient

<sup>†</sup> Data presented for BDI-II as odds ratio

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