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Relationship Between Intensive Care Unit Delirium Severity and 2-Year Mortality and Health Care Utilization

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Abstract

Objective: We hypothesized that higher severity of intensive care unit (ICU) delirium and greater days of delirium or coma would be associated with higher risk of mortality and shorter time to first Emergency Department (ED) visit and rehospitalization within 2 years after hospital discharge.

Methods: We performed a secondary data analysis of Pharmacological Management of Delirium and Deprescribe, randomized controlled trials designed to reduce ICU delirium. Patients were assessed twice daily for delirium or coma using the Richmond Agitation Sedation Scale and Confusion Assessment Method for the ICU (CAM-ICU). Delirium severity was calculated using the CAM-ICU-7. Mean delirium severity (from the time of randomization to discharge) was categorized as rapidly resolved, mild to moderate, or severe. We used Cox's proportional hazards regression to model time to death, the first ED visit, and rehospitalization. Analyses were adjusted for age, gender, race, Charlson comorbidity index, APACHE II, discharge location, diagnosis, and ICU type.

Results: Out of 434 patients, those with severe delirium had higher mortality risk than those with rapidly resolved delirium (HR 2.21, 95% CI, 1.35–3.61). Those who had 5 or more days of delirium or coma had higher mortality risk than those with less than 5 days of delirium or coma (HR 1.52, 95% CI, 1.07–2.17). Delirium severity and the number of days of delirium or coma were not associated with time to ED visits and rehospitalizations.

Conclusion: Higher delirium severity and more days of delirium or coma are associated with higher mortality risk 2 years after discharge.

INTRODUCTION

Delirium is defined as an acute change in mental status, characterized by inattention and fluctuating levels of consciousness.¹ Patients in the ICU due to severity of illness, multiple comorbidities, and exposure to sedative and analgesic medications^{3–6} are particularly vulnerable to develop delirium or coma.⁷ The prevalence of delirium in the ICU ranges from 60–87%.^{4,8,9} The healthcare costs associated with delirium in the intensive care unit (ICU) are estimated to be 20% higher than in non-delirious patients in the United States.²

Previous work has shown the importance of quantifying the duration and severity of delirium beyond identifying its presence. Longer delirium duration and higher severity have been associated with functional decline and higher mortality after 1 year.^{10–15} The Confusion Assessment for the ICU-7 (CAM-ICU-7) is a validated measure of ICU delirium severity with high internal reliability and high predictive validity.¹⁶ In this study, we hypothesize that higher severity of delirium, as measured by the CAM-ICU-7, and a greater number of days of delirium or coma would be associated with higher rates of mortality and emergency department (ED) visits and hospitalizations within 2 years after hospital discharge.⁷ We used delirium or coma days as our variable of interest, coma being the most severe disruption in arousal and awareness of brain dysfunction.

METHODS

Study design and setting

Patients who were admitted to the ICU services of three academic Indianapolis hospitals (Eskenazi, University, and Methodist) from February 2009 to January 2015 were enrolled in the Pharmacological Management of Delirium (PMD) and Deprescribe-PMD (de-PMD) studies, two parallel pragmatic randomized controlled trials. For the purpose of our study we only included patients from Eskenazi Hospital as they have complete healthcare utilization data. Patients alive at hospital discharge, who screened positive for delirium based on the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the ICU (CAM-ICU), were included in the secondary data analysis for this study. Details of the PMD and de-PMD trials have been reported previously.^{17, 18}

Measurements

Trained research assistants assessed patients for delirium twice a day, morning (9:00-11:00 am) and afternoon (3:00-5:00 pm), using the RASS and CAM-ICU from the first day of ICU admission until patients' discharge from the hospital or death.^{4,19,20} The RASS has excellent inter-rater reliability (interclass correlation = 0.956; k = 0.73, 95% CI, 0.71-0.75) and high validity in the adult ICU population.^{19, 20} Patients who scored a -4 or -5 with a lack of response to verbal or physical stimuli on the RASS were considered to be comatose and were not administered the CAM-ICU. Patients who scored -3 to +4 on the RASS were administered the CAM-ICU, which tests patients for acute or fluctuating changes in mental status, inattention, altered level of consciousness, and disorganized thinking.⁴

Delirium severity was calculated on a 7-point rating measure using the CAM-ICU-7, a validated measure derived from the CAM-ICU and RASS assessments with higher scores indicating higher severity of delirium.^{4, 16} Acute onset or fluctuation of mental status is scored 1 if it is present or 0 if absent. Inattention is scored from 0 to 2, 0 being absent and 2 for severe inattention. Altered level of consciousness, present if the RASS is other than zero (absent is 0), is scored 1 for RASS 1 or -1, and 2 for RASS >1, <-1. Disorganized thinking is scored from 0 to 2, 0 being absent and 2 severe disorganization.^{4,16} The CAM-ICU-7 has high internal reliability (Cronbach's alpha = 0.85) and high predictive validity of in-hospital mortality (OR = 1.47; 95% CI, 1.30–1.66) and lower odds of being discharged home (OR =0.8; 95% CI, 0.72–0.9).¹⁶ For each patient, delirium severity was calculated as the mean CAM-ICU-7 during the entire hospitalization. Although all patients had to be delirious at some point (*i.e.* no one could be comatose for the entire study), there could be timepoints during the ICU stay at which patients may have coma. Therefore, comatose scores were assigned an imputed value of 7 for delirium severity, the highest CAM-ICU-7 score, given that coma represents most severe disruption of arousal and awareness. As we did not expect the relationship between mean delirium severity and outcome variables to be linear, we categorized mean delirium severity into three groups: rapidly resolving delirium (mean CAM-ICU-7 0–2), mild to moderate delirium (mean CAM-ICU-7 2.01–5), and severe delirium (mean CAM-ICU-7 > 5). We assigned the term "rapidly resolving" to the 0-2group because this group included patients with more severe delirium but that resolved quickly. Likewise, we also categorized the number of days of delirium or coma into the following two groups: 0–4 days and 5+ days. We used the following criteria to assign a day as delirious, comatose or normal. On a given day, a patient was considered delirious if any CAM-ICU assessment was positive; comatose if no CAM-ICU assessments met criteria for delirium and at least one RASS assessment was considered comatose; and normal if no RASS/CAM-ICU assessments met criteria for delirium or coma, and at least one CAM-ICU was considered normal.

Additional Covariates

Severity of medical illness was measured using the Charlson Comorbidity Index (CCI), which predicts the 10-year survival rate, and the Acute Physiology and Chronic Health Evaluation (APACHE II), which rates ICU mortality on a range of 0–71 using a combination of physiological variables and chronic health conditions.^{21, 22} The Charlson Index score is a widely used and studied comorbidity scoring system. In the original study, the Charlson

Index score showed a strong association of a 2.3-fold increase in the 10-year risk of mortality for each increasing level of the comorbidity.²¹

Outcome variables

Data for mortality and acute healthcare utilization, determined in our study by emergency department visits and hospitalizations after discharge for the index hospitalization, were collected from the Indiana Network for Patient Care database (INPC). The INPC collects data from 100 hospitals, health networks, and insurance providers covering more than 18 million patients.²³

Statistical analyses

To assess the relationship between delirium severity, as well as the number of days of delirium or coma, and each outcome of interest (mortality, time to first ED visits, and hospitalizations), we used Cox proportional hazards regression to model the time to event during the 2 years post-discharge. For each outcome, the time to event was calculated in days from the date of hospital discharge to the date of the event. For patients who were alive 2 years from the date of discharge, their mortality event time was censored at 2 years. For patients without ED visits or hospitalizations, event times were censored using the minimum value of time to death or time to last utilization in the system. If both times were longer than 2 years, their event time was censored at 2 years. We used the Kolmogorov-type supremum test to test for nonproportional hazards.

All models were adjusted for age, gender, race, measures of severity of medical illness (CCI and APACHE II), discharge location, ICU diagnoses (acute respiratory failure, sepsis, neurologic disorders, and other), and type of ICU. Results were similar when data of patients that received an intervention were also included as a covariate, and therefore this variable was not included in the final models. Eight patients without a CAM-ICU-7 assessment or a RASS assessment post-randomization were excluded from the analysis. All analyses were performed using SAS v9.4.

RESULTS

A total of 434 patients of the 551 enrolled in the PMD and de-PMD studies were included in our study (Supplemental Figure 1). The mean age was 59.8 ± 16.4 years. More than half of the patients were female (54.6%). About half of the patients were African American (48.6%). The most common ICU admission diagnoses were acute respiratory failure and sepsis (47.9%). Almost two-thirds of the patients were hospitalized in the medical ICU (62.7%). (See Table 1.) We first examined the relationship between delirium severity and time to death, ED visits, and hospitalization. (See Figure 1.) The adjusted hazard ratio (HR; 95% CI) for mortality within 2 years after hospital discharge was calculated for groups separated by delirium severity (Table 2). Patients with severe delirium were more likely to die within 2 years after discharge than those with rapidly resolving delirium, while those with mild to moderate delirium did not appear to have a higher risk of death within 2 years after discharge (mild to moderate delirium, HR 1.08, 95% CI, 0.73–1.58 p = 0.710; severe delirium, HR 2.21, 95% CI, 1.35–3.61 p = 0.002). Older age, higher CCI, and APACHE II

scores were also associated with increased mortality within 2 years after hospital discharge (P < 0.05) (Supplemental Table 1). Delirium severity was not associated with the time to ED visits or hospitalizations within 2 years after hospital discharge (all P > 0.05).

We then examined the relationship between the number of days of delirium or coma and time to mortality, ED visits, and hospitalization. The adjusted HR (95% CI) for mortality within 2 years after hospital discharge was calculated for groups separated by the number of days of delirium or coma (Table 3). Compared to patients who had 4 days or less of delirium or coma, patients who had 5 or more days of delirium or coma were more likely to die within 2 years of hospital discharge (adjusted HR 1.52, 95% CI, 1.07–2.17, P = 0.019). (See Figure 2.) The number of days of delirium or coma was not associated with the risk of ED visits and hospitalization within 2 years after hospital discharge (all P > 0.05) (Table 3, Supplemental Table 2).

DISCUSSION

Our findings demonstrate that higher delirium severity is associated with an increased risk of mortality within 2 years after hospital discharge, even after adjusting for age and medical comorbidity. Likewise, patients with more days of delirium or coma had an increased risk of mortality within 2 years after hospital discharge. We also found that neither higher delirium severity nor number of delirium or coma days were associated with time to ED visits and hospitalizations.

Our results are consistent with previous studies showing that delirium is associated with a higher risk of mortality after discharge from the index hospitalization.^{12, 13, 24–26} However, the evidence about the relationship between delirium and mortality risk for ICU-based cohorts is conflicting. Ely et al. found that ICU delirium is associated with a higher risk of mortality after 1 month and 6 months.^{24,27,28} On the other hand, Wolters *et al.* found that ICU delirium was not associated with a higher risk of mortality at 1 year after discharge.²⁹ These prior studies explored the presence of delirium with long-term outcomes, whereas we are exploring the relationship between duration and severity and 2-year outcomes. Our results and prior work indicate that describing delirium as present or not might not be sufficient when exploring possible outcomes and further categorization based on severity or duration should be considered for prognostic purposes. Delirium severity is a powerful prognostic indicator that has also been associated with progressive cognitive decline.^{10,13–15} Measuring delirium severity could also prove useful to develop treatments targeted toward this in higher-risk populations. The relationship between ICU delirium severity and mortality at 2 years is novel and extends the findings of our prior study, which showed that higher delirium severity in the ICU is associated with higher in-patient mortality.¹⁶

The absence of a relationship between delirium severity and number of days of delirium or coma and our measure of healthcare utilization (ED visits and hospitalizations) differs from the earlier literature, which suggests a connection between delirium and healthcare utilization.^{10, 15} Delirium severity has been previously associated with increased nursing home placement.^{10, 15} Vasunilashorn *et al.* reported a lack of a significant association between delirium severity and readmissions.¹⁵ Brummel *et al.* found that longer delirium

duration in the ICU was associated with disability in activities of daily living (ADLs) in the year following index hospitalization.¹¹ Previous studies have not extensively examined the relationship between delirium severity and ED visits after hospital discharge. Future studies will also need to examine the association between delirium or coma with other types of healthcare utilization, such as home health aide services and rehabilitation, and loss of productivity for both patients and their caregivers. Limiting the delirium impact to ED admissions and hospitalizations may provide a crude look at best into delirium-associated morbidity and could miss other aspects of healthcare burdens that delirium imposes on patients.

The major strength of our study includes the use of a delirium severity tool that has been created for, and validated in, the ICU population.¹⁶ Examining delirium severity provides additional information on symptom burden/intensity, expanding on the traditional focus of delirium presence/absence. The study cohort was racially diverse, with about half being African American. One major limitation is that the study was conducted in a single hospital, which may limit the generalizability of our findings. Psychosocial factors and measures of caregiver stress, which are known to impact healthcare utilization in other populations, were also not captured. Finally, other measures of post-ICU healthcare utilization, such as placement in a skilled nursing facility, referral to rehabilitation care, or home-based services, and measures of post-ICU clinical outcomes, such as cognition and functional performance, were not collected.

CONCLUSION

Our study demonstrates that increased delirium severity and number of days of delirium or coma were associated with a higher 2-year risk for mortality but not healthcare utilization. Future studies will need to further explore whether increased delirium severity and delirium or coma days are associated with utilization of other types of healthcare services and other clinical outcomes, including cognitive functioning, physical functioning, mental health functioning, falls, and frailty. Finally, future work also needs to collect data about psychosocial factors, such as caregiver stress, which are known to contribute to healthcare costs and increased hospitalization rates in other populations.³⁰

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

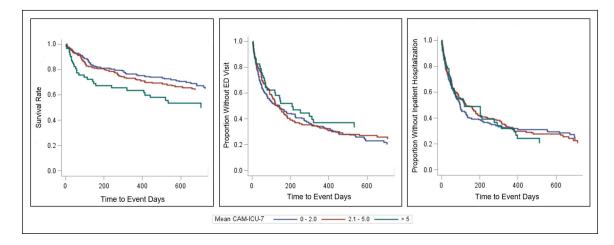
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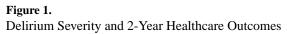
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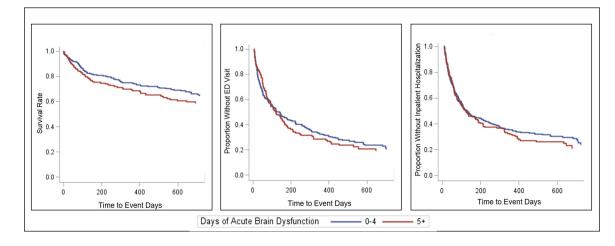


Figure 2.

Delirium or Coma and Healthcare Outcomes

Table 1.

Demographic and Clinical Characteristics of ICU Cohort

Characteristics	ICU Cohort (<i>N</i> = 434)		
Mean Age (SD)	59.8 (16.4)		
% Female (n)	54.6 (237)		
Race-Ethnicity			
% African-American (n)	48.6 (210)		
% Caucasian (n)	50.0 (216)		
% Asian (n)	0.2 (1)		
% Hispanic (n)	1.2 (5)		
Diagnosis			
% ARF/Sepsis (n)	47.9 (208)		
% Neurologic/Altered Mental Status (n)	15.2 (66)		
% Other (n)	36.9 (160)		
Unit			
% MICU (n)	62.7 (272)		
% PICU (n)	12.0 (52)		
% SICU (n)	25.3 (110)		
Mean Charlson (SD)	2.9 (2.6)		
Mean APACHE II (SD)	19.5 (8.1)		
Days of Delirium or Coma			
0-4	58.3 (253)		
5–9	24.0 (104)		
10+	17.7 (77)		
Mean CAM-ICU-7			
0-2 (rapidly resolving)	42.2 (183)		
2.1-5 (mild to moderate)	43.3 (188)		
> 5 (severe)	14.5 (63)		
Death			
% within 2 Years (n)	33.0 (143)		
ED visits			
% within 2 Years (n)	63.8 (277)		
Inpatient admissions	· · · · ·		
% within 2 Years (n)	65.0 (282)		

ICU = intensive care unit. SD = standard deviation. ARF = acute respiratory failure. MICU = medical ICU. PICU = progressive (step-down) ICU. SICU = surgical ICU. ED = emergency department.

APACHE II score range 0-71. Increasing score is associated with increasing risk of hospital death.

Charlson Comorbidity Index score of 2 indicates 90% survival at 10 years. A score of 3 indicates 77% survival at 10 years.

Continuous and discontinuous variables are measured as mean (SD).

Table 2.

Adjusted Proportional Hazards Model Results for Delirium Severity with Outcomes

	Mortality	ED Visits	Hospitalizations
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Mean CAM-ICU-7*			
0–2 (reference)	1.00	1.00	1.00
2.1–5	1.08 (0.73, 1.58)	0.87 (0.67, 1.13)	0.91 (0.70, 1.18)
> 5	2.21 (1.35, 3.61)	0.83 (0.56,1.24)	0.96 (0.65, 1.42)

ED = emergency department. HR = hazard ratio. CI = confidence interval

*Timepoints for which patients were comatose were assigned the highest CAM-ICU-7 score of 7.

Models were adjusted for age, gender, race, measures of severity of medical illness (CCI and APACHE II), discharge location, ICU diagnoses (acute respiratory failure, sepsis, neurologic disorders, and other), and type of ICU.

Adjusted Proportional Hazards Model Results for Days of Delirium or Coma with Outcomes

	Mortality	ED Visits	Hospitalizations
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Days of Delirium or Coma			
0-4 (reference)	1.00	1.00	1.00
5+	1.52 (1.07, 2.17)	1.06 (0.82, 1.37)	1.12 (0.87, 1.44)

ED = emergency department. HR = hazard ratio. CI = confidence interval.

Models were adjusted for age, gender, race, measures of severity of medical illness (CCI and APACHE II), discharge location, ICU diagnoses (acute respiratory failure, sepsis, neurologic disorders, and other), and type of ICU.