Delirium Management

RELATIONSHIP BETWEEN INTENSIVE CARE UNIT DELIRIUM SEVERITY AND 2-YEAR MORTALITY AND HEALTH CARE UTILIZATION

By Patricia S. Andrews, MD, Sophia Wang, MD, Anthony J. Perkins, MS, Sujuan Gao, PhD, Sikandar Khan, DO, MS, Heidi Lindroth, PhD, RN, Malaz Boustani, MD, MPH, and Babar Khan, MD, MS

Background Critical care patients with delirium are at an increased risk of functional decline and mortality long term.

Objective To determine the relationship between delirium severity in the intensive care unit and mortality and acute health care utilization within 2 years after hospital discharge.

Methods A secondary data analysis of the Pharmacological Management of Delirium and Deprescribe randomized controlled trials. Patients were assessed twice daily for delirium or coma using the Richmond Agitation-Sedation Scale and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Delirium severity was measured using the CAM-ICU-7. Mean delirium severity (from time of randomization to discharge) was categorized as rapidly resolving, mild to moderate, or severe. Cox proportional hazards regression was used to model time to death, first emergency department visit, and rehospitalization. Analyses were adjusted for age, sex, race, Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation II score, discharge location, diagnosis, and intensive care unit type.

Results Of 434 patients, those with severe delirium had higher mortality risk than those with rapidly resolving delirium (hazard ratio 2.21; 95% CI, 1.35-3.61). Those with 5 or more days of delirium or coma had higher mortality risk than those with less than 5 days (hazard ratio 1.52; 95% CI, 1.07-2.17). Delirium severity and number of days of delirium or coma were not associated with time to emergency department visits and rehospitalizations.

Conclusion Increased delirium severity and days of delirium or coma are associated with higher mortality risk 2 years after discharge. (American Journal of Critical Care. 2020;29:311-317)

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Delirium is defined as an acute change in mental status, characterized by inattention and fluctuating levels of consciousness. Patients in the intensive care unit (ICU) are particularly vulnerable to delirium or coma developing because of their severity of illness, multiple comorbidities, and exposure to sedative and analgesic medications. The prevalence of delirium in the ICU ranges from 60% to 87%. The health care costs associated with delirium in the ICU could be 20% higher than in nondelirious patients if not for the association of delirium with early ICU mortality in the United States.

Previous work has shown the importance of quantifying the duration and severity of delirium beyond identifying its presence. Longer delirium duration and greater severity have been associated with greater functional decline and higher mortality after 1 year. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is a validated measure of ICU delirium severity with high internal reliability and high predictive validity. In this study, we hypothesized that greater severity of delirium, as measured by the CAM-ICU, and a greater number of days of delirium or coma would be associated with higher rates of mortality and emergency department (ED) visits and rehospitalizations within 2 years after hospital discharge.

We used delirium or coma days as our variable of interest, coma being the most severe disruption of brain function in terms of arousal and awareness.

Methods

Study Design and Setting

Patients who were admitted to the ICU services of 3 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, 2 parallel pragmatic randomized controlled trials. For our study, we included only patients from Eskenazi Hospital, for whom complete health care utilization data were available. Patients alive at hospital discharge who screened positive for delirium using the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) were included in the secondary data analysis for this study. Details of the PMD and de-PMD trials have been reported previously.

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. The RASS has excellent interrater reliability (interclass correlation coefficient, 0.956; k = 0.73, 95% CI, 0.71-0.75) and high validity in the adult ICU population. 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.
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. 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, with 0 indicating absent and 2 indicating severe inattention. Altered level of consciousness, present if the RASS score is other than 0 (absent is 0), is scored 1 for a RASS score of 1 or −1 and 2 for a RASS score of greater than 1 or less than −1. Disorganized thinking is scored from 0 to 2, with 0 indicating absent and 2 indicating severe disorganization. The CAM-ICU-7 has high internal reliability (Cronbach α = 0.85) and high predictive validity for in-hospital mortality (odds ratio 1.47; 95% CI, 1.30–1.66) and lower odds of being discharged home (odds ratio 0.8; 95% CI, 0.72–0.9). 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 (ie, no one could be comatose for the entire study), there could be time points during the ICU stay at which patients had coma. Therefore, comatose scores were assigned an imputed value of 7 for delirium severity, the highest CAM-ICU-7 score, given that coma represents the most severe disruption of arousal and awareness. Because we did not expect the relationship between mean delirium severity and outcome variables to be linear, we categorized mean delirium severity into 3 groups: rapidly resolving delirium (mean CAM-ICU-7 score < 2), mild to moderate delirium (mean CAM-ICU-7 score 2.01–5), and severe delirium (mean CAM-ICU-7 score > 5). We assigned the term rapidly resolving to the 0 to 2 group because this group included patients with more severe delirium but whose delirium resolved quickly. Likewise, we categorized the number of days of delirium or coma into the following 2 groups: 0 to 4 days and 5 or more 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 1 RASS assessment was considered comatose; and normal if no RASS or CAM-ICU assessments met criteria for delirium or coma and at least 1 CAM-ICU assessment 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 II (APACHE II), which rates ICU mortality from 0 to 71 using a combination of physiological variables and chronic health conditions. The CCI is a widely used and studied comorbidity scoring system. In the original study, the CCI showed a strong association of a 2.3-fold increase in the 10-year risk of mortality for each increasing level of comorbidity.

Outcome Variables

Data for mortality and acute health care utilization, determined in our study by ED visits and rehospitalizations after discharge for the index hospitalization, were collected from the Indiana Network for Patient Care database. The Indiana Network for Patient Care collects data from 100 hospitals, health networks, and insurance providers covering more than 18 million patients.

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, ED visits, and rehospitalizations), we used Cox proportional hazards regression to model the time to event during the 2 years after 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 rehospitalizations, event times were censored using the minimum value of time to death or time to last healthcare 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, sex, race, measures of severity of medical illness (CCI and APACHE II score), discharge location, ICU diagnoses (acute respiratory failure, sepsis, neurologic disorders, and other), and type of ICU. Results were similar when data of patients who 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 after randomization were excluded from the analysis. All analyses were performed using SAS version 9.4.

Results

A total of 434 patients of the 551 enrolled in the PMD and de-PMD studies were included in our
study (see Supplemental Figure, available online only at www.ajcconline.org). The mean (SD) age was 59.8 (16.4) years. More than half of the patients were female (54.6%). About half of the patients (48.6%) were African American. 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%; Table 1).

We first examined the relationship between delirium severity and time to death, ED visits, and hospitalization (Figure 1). The adjusted hazard ratio (HR; 95% CI) for mortality within 2 years after hospital discharge was calculated for groups according to delirium severity (Table 2). Patients with severe delirium were more likely to die within 2 years after discharge than those with rapidly resolving delirium, whereas 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, \( P = .71 \); severe delirium, HR 2.21, 95% CI, 1.35-3.61, \( P = .002 \)). Older age, higher CCI, and higher APACHE II scores were also associated with increased mortality within 2 years after hospital discharge (all \( P < .05 \)) (see Supplemental Table 1, available online only). Delirium severity was not associated with the time to ED visits or hospitalizations within 2 years after hospital discharge (all \( P > .05 \)).

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 according to the number of days of delirium or coma (Table 3). Compared with 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 = .02; 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 > .05) (Table 3; Supplemental Table 2, available online only).

Discussion

Our findings demonstrate that greater 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 delirium severity nor number of delirium or coma days was 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. However, the evidence on the relationship between delirium and mortality risk for ICU-based cohorts is conflicting. Han et al., Ely et al., and Singh et al. found that ICU delirium is associated with a higher risk of mortality after 1 month and 6 months. 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. These previous studies explored the presence of delirium with long-term outcomes, whereas we explored the relationship between duration and severity and 2-year outcomes. Our results and previous work indicate that describing delirium as present or not may 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. Measuring delirium severity could also prove useful in developing treatments targeted

### Table 2

<table>
<thead>
<tr>
<th>Delirium severity</th>
<th>Mortality Hazard ratio (95% CI)</th>
<th>ED visits Hazard ratio (95% CI)</th>
<th>Hospitalizations Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 (reference)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2.1-5</td>
<td>1.08 (0.73-1.58)</td>
<td>0.87 (0.67-1.13)</td>
<td>0.91 (0.70-1.18)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>2.21 (1.35-3.61)</td>
<td>0.83 (0.56-1.24)</td>
<td>0.96 (0.65-1.42)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CAM-ICU-7, Confusion Assessment Method for the Intensive Care Unit-7; ED, emergency department; ICU, intensive care unit.

### Table 3

<table>
<thead>
<tr>
<th>Days of delirium or coma</th>
<th>Mortality Hazard ratio (95% CI)</th>
<th>ED visits Hazard ratio (95% CI)</th>
<th>Hospitalizations Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 (reference)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 5</td>
<td>1.52 (1.07-2.17)</td>
<td>1.06 (0.82-1.37)</td>
<td>1.12 (0.87-1.44)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ED, emergency department; ICU, intensive care unit.

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**Figure 2** Delirium or coma and health care outcomes.

Abbreviation: ED, emergency department.
toward cognitive decline in higher-risk populations. The relationship between ICU delirium severity and mortality at 2 years is a novel finding and extends the findings of our previous study, which showed that greater delirium severity in the ICU is associated with higher inpatient mortality.16

The absence of a relationship between delirium severity and number of days of delirium or coma and our measure of health care utilization (ED visits and hospitalizations) differs from earlier findings suggesting a connection between delirium and health care utilization.10,15 Delirium severity has been previously associated with increased nursing home placement.10,15 Vasunilashorn et al15 reported a lack of a significantly associated with increased nursing home placement in activities of daily living in the year following index hospitalization. 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 and other types of health care 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 at best a crude look at delirium-associated morbidity and could miss other aspects of health care burdens that delirium imposes on patients.

A major strength of our study is 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 and intensity, expanding on the traditional focus of delirium presence or 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 affect health care utilization in other populations, were also not captured. Finally, other measures of post-ICU health care 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 of mortality but not health care utilization. Future studies will need to explore further whether increased delirium severity and delirium or coma days are associated with utilization of other types of health care services and other clinical outcomes, including cognitive functioning, physical functioning, mental health functioning, falls, and frailty. Finally, future work also needs to include collection of data about psychosocial factors, such as caregiver stress, that are known to contribute to health care costs and increased hospitalization rates in other populations.30

FINANCIAL DISCLOSURES

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REFERENCES


SEE ALSO

For more about delirium in the intensive care unit, visit the Critical Care Nurse website, www.ccnonline.org, and read the article by Ungarian et al, “Delirium in the Intensive Care Unit: Is Dexmedetomidine Effective?” [August 2019].

Downloaded from https://ajccnonline.org/ajcconline/article-pdf/29/4/316/129497/316.pdf by guest on 10 August 2020


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### Supplemental Table 1
Proportional hazards model results for delirium severity covariate results with outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mortality (Hazard ratio 95% CI)</th>
<th>ED visits</th>
<th>Hospitalizations</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>1.02 (1.01-1.03)</td>
<td>0.99 (0.98-1.00)</td>
<td>1.01 (1.01-1.02)</td>
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<td>Female</td>
<td>1.30 (0.90-1.85)</td>
<td>1.17 (0.91-1.50)</td>
<td>1.06 (0.82-1.37)</td>
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<tr>
<td>African American</td>
<td>1.02 (0.72-1.44)</td>
<td>1.19 (0.93-1.52)</td>
<td>0.92 (0.72-1.17)</td>
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<td>Charlson Comorbidity Index</td>
<td>1.18 (1.11-1.25)</td>
<td>1.12 (1.06-1.17)</td>
<td>1.12 (1.06-1.18)</td>
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<td>APACHE II score</td>
<td>1.03 (1.01-1.06)</td>
<td>1.00 (0.98-1.02)</td>
<td>1.02 (1.00-1.03)</td>
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<td>Discharge home</td>
<td>0.88 (0.59-1.31)</td>
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<td>Diagnosis</td>
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<tr>
<td>ARF/sepsis</td>
<td>1.07 (0.71-1.62)</td>
<td>1.13 (0.84-1.51)</td>
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<td>Neurologic</td>
<td>1.14 (0.68-1.91)</td>
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<td>Other (reference)</td>
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<tr>
<td>Medical</td>
<td>0.94 (0.55-1.60)</td>
<td>0.92 (0.66-1.29)</td>
<td>0.84 (0.61-1.18)</td>
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<td>Progressive (step-down)</td>
<td>1.27 (0.65-2.46)</td>
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<td>Surgical (reference)</td>
<td>1.00</td>
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### Supplemental Table 2
Proportional hazards model results for days of acute brain dysfunction covariate results with outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mortality (Hazard ratio 95% CI)</th>
<th>ED visits</th>
<th>Hospitalizations</th>
</tr>
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<tr>
<td>Age</td>
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<td>Female</td>
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<td>African American</td>
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<td>Charlson Comorbidity Index</td>
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<tr>
<td>APACHE II score</td>
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<td>Discharge home</td>
<td>0.90 (0.60-1.34)</td>
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<td>ARF/sepsis</td>
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<td>Neurologic</td>
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<td>Other (reference)</td>
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<tr>
<td>Medical</td>
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<td>Progressive (step-down)</td>
<td>1.41 (0.73-2.74)</td>
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<td>Surgical (reference)</td>
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<td>1.00</td>
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</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARF, acute respiratory failure; ED, emergency department.

### Supplemental Figure
Flow of participants through study.

Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; de-PMD, Deprescribe-Pharmacological Management of Delirium; PMD, Pharmacological Management of Delirium; RASS, Richmond Agitation-Sedation Scale.

Patients enrolled in PMD and de-PMD trials (n=551)

- Excluded: Died at discharge (n=71)
- Withdrew from the study (n=7)
- Patients from 2 other hospitals (n=31)
- No RASS/CAM-ICU assessment after randomization (n=8)

Included in analysis (n=434)