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Dynamic Delirium Severity Trajectories and Their Association With 2-Year Healthcare Utilization and Mortality Outcomes

Heidi Lindroth, PhD, RN[1–3]
Sanjay Mohanty, MD[4]
Damaris Ortiz, MD[5,6]
Sujuan Gao, PhD[7]
Anthony J. Perkins, MS[7]
Sikandar H. Khan, DO[3,6,8]
Malaz A. Boustani, MD, MPH[2,3,9,10]
Babar A. Khan, MD, MS[2,3,8,9,10]

IMPORTANCE: Delirium severity has been associated with a higher risk of mortality and an increasing morbidity burden. Recently defined delirium severity trajectories were predictive of 30-day mortality in a critically ill patient population. No studies to date have examined associations between delirium severity trajectories and 2-year mortality and healthcare utilization outcomes.

OBJECTIVES: To examine the associations between recently defined delirium severity trajectories and 2-year healthcare utilization outcomes of emergency department visits, rehospitalizations, and mortality.

DESIGN, SETTING, AND PARTICIPANTS: This is a secondary analysis using data from the randomized controlled clinical trial Pharmacological Management of Delirium in the Intensive Care Unit and Deprescribing in the Pharmacologic Management of Delirium trial conducted from 2009 to 2015. Patients who were greater than or equal to 18 years old, were in the ICU for greater than or equal to 24 hours, and had a positive delirium assessment (Confusion Assessment Method for the ICU) were included in the original trial. Participants were included in the secondary analysis if 2-year healthcare utilization and mortality data were available ($n = 431$).

MAIN OUTCOMES AND MEASURES: Healthcare utilization data within 2 years of the initial discharge date were pulled from the Indiana Network for Patient Care. Data over a 2-year period on emergency department visits (days to first emergency department visit, number of emergency department visits), inpatient hospitalizations (days to first hospitalizations, number of hospitalizations), and mortality (time to death) were extracted. Univariate relationships, Cox proportional hazard models, and competing risk modeling were used to examine statistical relationships in SAS v9.4.

RESULTS: The overall sample ($n = 431$) had a mean age of 60 (SD, 16), 56% were females, and 49% African-Americans. No significant associations were identified between delirium severity trajectories and time to event for emergency department visit, mortality, or rehospitalization within 2 years of the index hospital discharge.

CONCLUSIONS AND RELEVANCE: This secondary analysis did not identify a significant relationship between delirium severity trajectories and healthcare utilization or mortality within 2 years of hospital discharge.

KEY WORDS: delirium; delirium severity; healthcare utilization; mortality; trajectories

Up to 80% of mechanically ventilated, critically ill patients suffer from delirium, a type of acute brain failure (1, 2). The risk of mortality, institutionalization, and cognitive impairment parallels the severity of delirium; as delirium severity increases, so does the risk of these adverse outcomes (3, 4). Further, the clinical course, or trajectory, of delirium severity is important to consider as shown by our recently published study. We defined five

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distinct trajectories of delirium severity and showed that belonging to a specific trajectory is predictive of 30-day mortality (5). The five trajectories of delirium severity encapsulate two key components of delirium: the fluctuation of symptoms and the duration of these symptoms. The trajectories capture a 7-day clinical period and are defined as follows: "Mild-Brief" (mild to no delirium symptoms), "Mild-Accelerating" (mild delirium symptoms that accelerated to severe delirium), "Severe-Rapid Recovers" (severe delirium with rapidly resolving severity), "Severe-Slow Recovers" (sustained severe delirium with resolution to mild delirium over the 7-d period), and "Severe-Nonrecovers" (sustained severe delirium) (2). Beyond the relationship with 30-day mortality, further associations between the trajectory of delirium severity and healthcare outcomes after the index hospital discharge are not well described.

A recent study reported that ICU survivors accessed the healthcare system at an increased rate 2 years following their initial hospital discharge when compared with their pre-ICU healthcare use (6). The study did not investigate whether ICU markers of illness, such as delirium severity and duration or the trajectories of delirium severity, influence post-ICU healthcare utilization. Elucidating how different trajectories of delirium severity are related to healthcare utilization 2 years following index hospital discharge may highlight opportunities to provide supportive therapies and resources.

The primary aim of this study was to examine the association between delirium severity trajectories and 2-year healthcare utilization in terms of emergency department (ED) visits and hospitalizations among ICU survivors. The second aim was to investigate the ability of these dynamic delirium severity trajectories to predict 2-year mortality. We hypothesized that healthcare utilization patterns would significantly vary between trajectories.

METHODS

This is a secondary analysis using data from two pragmatic randomized controlled trials (NCT00842608) conducted from 2009 to 2015 (7, 8). Patients enrolled in either clinical trial during their index ICU admission and subsequently discharged alive were included in this study. The 2-year healthcare utilization and mortality data post hospital discharge were extracted from the Indiana Network for Patient Care (INPC), a statewide medical records data repository. Patients without healthcare utilization or mortality data reported in INPC were excluded. In the original trials, patients were greater than or equal to 18 years old, were in the ICU for greater than or equal to 24 hours, and had a positive delirium assessment using the Confusion Assessment Method for the ICU (CAM-ICU) and delirium severity measured using the CAM-ICU-7. Exclusion criteria and the main results of these two trials have been previously published (7, 8). This analysis was deemed exempt by the Indiana University Institutional Review Board (number 1812764150). Reporting on the analysis followed the **Supplementary Strobe Checklist** (http://links.lww.com/CCX/A794).

Clinical Measurements

Delirium severity trajectories serve as the primary exposure variable for this analysis. These trajectories were previously defined and summarize a 7-day period of delirium severity, starting at enrollment into the original trial (5). The delirium severity measurement tool used to define these trajectories was the CAM-ICU-7 (3). This was administered by trained study team members over a 7-day clinical period that started upon enrollment into the parent trials. All delirium severity and acute brain failure measurements obtained during that 7-day period were integrated into the defined trajectories (n = 4,438 assessments; n = 531 participants). Coma was defined as a Richmond Agitation and Sedation Scale score of –4 or –5 and was included in the trajectories as severe delirium (CAM-ICU-7 score of 7) as it represents a severe form of acute brain failure. CAM-ICU-7 scores range from 0, indicating no delirium, to 7, indicating severe delirium (3).

Other data included demographics (age, sex, race), illness severity defined by Acute Physiology and Chronic Health Evaluation (APACHE) II, comorbidities quantified by Charlson Comorbidity Index (CCI), baseline cognitive function using the Informant Questionnaire on Cognitive Decline in the Elderly, and functional status using the Instrumental Activities of Daily Living. These were completed through a combination of chart review and legally authorized representative, or proxy, questionnaire completion.

Outcome Measurements

The total number of and time to first ED visit and inpatient hospitalization were defined as the healthcare utilization outcomes. The timeframe for data extraction was defined

as the discharge date of the initial index hospitalization to 2 years after that discharge date. Healthcare utilization and mortality data were extracted from the INPC database. The INPC database is a statewide data repository that contains medical records from 90% of Indiana's hospitals and encompasses two thirds of Indiana's population (9). In addition, the statistician (A.J.P.), who has expertise in working with INPC data, performed quality checks to ensure complete data capture.

Statistical Analysis

Demographic, clinical characteristics, healthcare utilization, and mortality were summarized using descriptive statistics. Nonparametric Kruskal-Wallis, one-way analysis of variance, and chi-square tests examined bivariate relationships (medians and frequencies) between trajectories and outcomes (number of ED visits and hospitalizations, percentage of ED visits, hospitalizations, and mortality). Cox proportional hazard and competing risk models examined the association between the delirium severity trajectories and time to mortality, first ED visit, and hospitalization. The time to event was calculated in days from the date of hospital discharge to the date of the event. Patients who did not have an event (death, ED, or hospitalization) were censored at time of last utilization in the system or at 2 years (730 d). Patients who died prior to an event (ED and/or hospitalization) were censored at time of death. The final sample size of the analyses was *n* equals to 431 (*n* = 67 had in-hospital mortality, *n* = 33 did not have healthcare utilization data available in the INPC database) (**Supplementary Fig. 1**, http://links.lww.com/CCX/A763). **Supplementary Table 1** (http://links.lww.com/CCX/A763) displays the estimated survival time to event per trajectory for each outcome.

Survival models (Cox proportional hazard and competing risk models) were adjusted for age, sex, race, and comorbidities. These were collected upon enrollment into the pharmacologic management of delirium (PMD) trials, during initial hospitalization, and were included in this analysis as they are common confounders for increased healthcare utilization and mortality. The assumptions of the Cox proportional hazard models were verified. All analyses were completed using SAS v9.4. Significance was noted at *p* value of less than 0.05.

Two sensitivity analyses were completed. First, those who died at or before day 30 were removed from the analysis, and the models were reanalyzed. Second, trajectories that shared similar hazard ratios in the proportional hazard modeling procedures were combined (trajectories "Severe-Rapid Recovers" and "Severe-Slow Recovers" were combined, trajectories "Mild-Accelerating and Severe-Nonrecovers" were combined) and reanalyzed.

RESULTS

The overall cohort (*n* = 431) had a mean age of 60 years (SD, 16), 56% female, and 49% African-American. During the original hospitalization, 73% were mechanically ventilated with a mean APACHE II score of 19.5 (SD, 8.1) and CAM-ICU-7 score of 3.6 (SD, 2.2). **Table 1** describes the overall demographics, clinical characteristics, healthcare utilization, and mortality of the cohort within the delirium severity trajectories. Randomization to intervention or control groups in the original studies was not significant between delirium severity trajectories.

No significant associations were identified between the delirium severity trajectories and the number of ED visits or hospitalizations (Table 1).

The results of the survival analyses are shown in **Table 2** and **Figure 1**. No significant associations were identified between delirium severity trajectories and time to event for ED visit, mortality, or rehospitalization in either the Cox proportional hazard models or the competing risk models. Neither sensitivity analysis modified the above results.

DISCUSSION

This analysis examined the association between delirium severity trajectories and the utilization of healthcare and mortality at 2 years. No associations were identified between the delirium severity trajectories and 2-year healthcare utilization or mortality.

A recent study from this cohort did report a significant relationship between severe delirium (CAM-ICU-7 mean > 5) and the risk of mortality at 2 years (10). This study used all available delirium severity data through the hospital stay and categorized the CAM-ICU-7 scores into rapidly resolving (CAM-ICU-7 score 0–2), moderate (2.1–5), and severe (> 5). This contrasts with our current analysis which used delirium severity trajectories defined from the first 7-day period following study enrollment. The difference between the time periods (overall hospital

TABLE 1.
Clinical Characteristics and Healthcare Utilization Overall and by Trajectory/Phenotype

Cohort Characteristics	Full Cohort (*N* = 431)	Mild-Brief (*N* = 79)	Severe-Rapid Recovery (*N* = 74)	Mild-Accelerating (*N* = 23)	Severe-Slow Recovery (*N* = 89)	Severe-Nonrecovers (*N* = 166)
Demographics						
Age, mean ± SD	60 ± 16	59 ± 16	59 ± 16	65 ± 14	58 ± 15	61 ± 17
Female, % (*n*)	55 (235)	57 (45)	50 (37)	57 (13)	49 (44)	58 (96)
Caucasian, % (*n*)	51 (220)	66 (52)	56 (42)	57 (13)	47 (42)	43 (71)
African-American[a], % (*n*)	49 (209)	34 (26)	44 (32)	43 (10)	53 (47)	57 (94)
Clinical data						
Acute Physiology and Chronic Health Evaluation II, mean ± SD	19.5 ± 8.1	19.7 ± 9.1	19.1 ± 7.8	19.0 ± 9.3	19.5 ± 8.2	19.7 ± 7.5
Charlson Comorbidity Index, mean ± SD	2.9 ± 2.6	2.7 ± 2.5	3.4 ± 2.8	2.4 ± 1.9	2.9 ± 2.7	2.9 ± 2.6
Informant Questionnaire on Cognitive Decline in the Elderly[a], mean ± SD	3.2 ± 0.5	3.1 ± 0.4	3.2 ± 0.4	3.5 ± 0.6	3.1 ± 0.3	3.3 ± 0.5
Instrumental Activities of Daily Living[a], mean ± SD	6.2 ± 2.6	6.8 ± 2.1	6.1 ± 2.5	5.7 ± 2.8	6.7 ± 2.3	5.8 ± 2.8
Confusion Assessment Method for the ICU-7[a], mean ± SD	3.6 ± 2.2	0.4 ± 0.4	2.1 ± 0.9	2.2 ± 0.8	3.8 ± 0.9	5.8 ± 1.0
Mechanical ventilation[a], % (*n*)	74 (318)	70 (55)	77 (57)	43 (10)	79 (70)	78 (126)
Coma days[a], % (*n*)	0.9 ± 1.3	0.0 ± 0.0	0.3 ± 0.5	0.3 ± 0.6	0.8 ±0.9	1.7 ± 1.6
Discharge to home[a], % (*n*)	41 (177)	65 (51)	46 (34)	26 (6)	38 (34)	31 (52)
Outcomes, % (*n*)						
Emergency department visits	64 (274)	67 (53)	73 (54)	48 (11)	65 (58)	59 (98)
Hospitalized	65 (281)	62 (49)	69 (51)	52 (12)	67 (60)	66 (109)
30-d mortality[a]	4 (17)	1 (1)	3 (2)	13 (3)	2 (2)	5 (9)
2-yr mortality	33 (141)	27 (21)	32 (24)	43 (10)	28 (25)	37 (61)

Welch's test of means allowing for unequal variances and analysis of variance ([a]significant differences between trajectories): Lawton-Instrumental Activities of Daily Living ($p = 0.01$), Informant Questionnaire on Cognitive Decline in the Elderly ($p < 0.001$), Confusion Assessment Method for the ICU-7 (CAM-ICU-7) mean ($p < 0.001$), CAM-ICU-7 variation ($p < 0.001$), Richmond Agitation and Sedation Scale ($p < 0.001$), and coma days ($p < 0.001$). χ^2 for binary.

Presents the overall study demographic, clinical characteristics, healthcare utilization, and mortality of the overall cohort and within each trajectory. Thirty-day mortality represents those who discharged alive from the index hospitalization and died prior to day 30 post discharge.

TABLE 2.
Hazard Ratios (95% CIs) From Cox Proportional Hazard Models

	Mortality		Emergency Department Visits		Hospitalizations	
	Adjusted		Adjusted		Adjusted	
Trajectory						
Mild-Brief	Reference	Reference	Reference	Reference	Reference	Reference
Severe-Rapid Recovery	1.36 (0.76–2.45)	1.13 (0.61–2.12)	1.31 (0.90–1.91)	1.17 (0.78–1.75)	1.27 (0.86–1.88)	1.20 (0.79–1.82)
Mild-Accelerating	2.00 (0.94–4.25)	1.38 (0.60–3.14)	0.76 (0.40–1.45)	0.86 (0.44–1.68)	0.87 (0.46–1.63)	0.64 (0.33–1.27)
Severe-Slow Recovery	1.15 (0.65–2.06)	1.00 (0.53–1.85)	1.15 (0.80–1.68)	1.08 (0.73–1.61)	1.32 (0.90–1.92)	1.20 (0.80–1.80)
Severe-Nonrecovers	1.66[a] (1.01–2.72)	1.20 (0.69–2.09)	0.97 (0.69–1.35)	0.92 (0.63–1.33)	1.23 (0.88–1.72)	1.02 (0.70–1.48)

[a]Statistical significance $p < .05$.

Table 2 reports the hazard ratios (95% CIs) on the unadjusted (trajectories only) and adjusted models. Models were adjusted for age, sex, race, comorbidities (Charlson Comorbidity Index), illness severity (Acute Physiology and Chronic Health Evaluation, APACHEII), baseline cognition (Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE) and function (Instrumental Activities of Daily Living), ICU service (Medical, Surgical, and Progressive Care ICUs), diagnosis code, and discharge disposition (home vs institution).

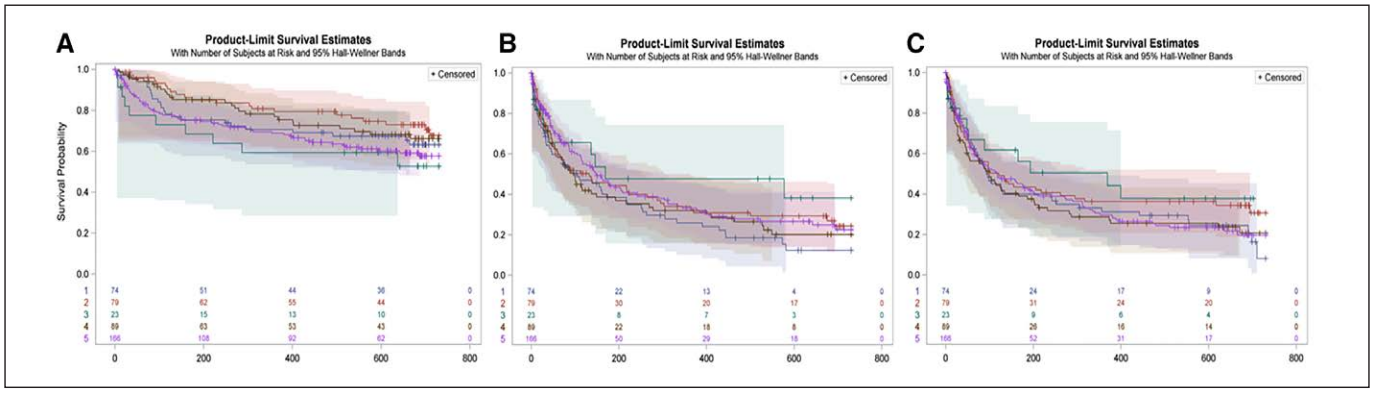

Figure 1. Illustrates survival plots for each 2-yr outcome: time to death (**A**), time to first emergency department visit (**B**), and time to first inpatient hospitalization (**C**). Time to event was calculated in days for the date of the index hospital discharge to the date of the event. Individuals who did not have an event were either censored at time of last utilization in the system or at 2 yr (730 d). Individuals who died prior to an emergency department visit or hospitalization were censured at the time of death. Trajectory key: 1) *Blue*—Severe-Rapid Recovery, 2) *Red*—Mild-Brief, 3) *Teal*—Mild-Accelerating, 4) *Brown*—Severe-Slow Recovery, and 5) *Pink*—Severe-Nonrecovers.

duration vs 7-d) may highlight the importance of cumulative exposure to severe delirium as a function of more hospital days along with a greater risk of exposure to other hospital-acquired conditions. Further, patients who survived past hospital day 7 are likely different from those who experienced mortality in the immediate hospital period. In the original delirium severity trajectory analysis, both the "Mild-Accelerating" and the "Severe-Nonrecovers" trajectories had a significantly higher in-hospital mortality rate, 20% and 14%, respectively. Following adjustment for age, race, sex, illness severity, comorbidities, and baseline cognitive and function, the "Mild-Accelerating" trajectory was significantly associated with 30-day mortality ($p < 0.001$) (5). The participants within this trajectory were older and had lower baseline function and cognition. This particular delirium severity trajectory may highlight not only the importance of baseline vulnerability to delirium but how the short-term exposure and acceleration to severe delirium in

vulnerable individuals may expedite the likelihood of short-term adverse outcomes. Following this reasoning, the current delirium severity trajectories may be better suited to the prediction of short-term outcomes (30-d mortality) as the exposure time is set at 7 days and does not incorporate the cumulative exposure of a longer hospital stay. Therefore, the full delirium burden during hospitalization may be a better predictor of long-term outcomes. Future studies should investigate lengthening the exposure time of the delirium severity trajectories to better capture the full delirium burden of hospital survivors. Previous studies have shown that a higher burden of physical and mental health comorbidities drives healthcare utilization in terms of ED use, hospitalizations, and mortality in multiple patient populations (11–14). In this analysis, the CCI was a significant confounder in Cox proportional hazard models for 2-year ED use, hospitalizations, and mortality. Although several studies have reported a significant relationship between mortality and delirium severity and duration, it is not well established how delirium contributes to the overall physical and mental health morbidity burden in terms of chronic disease. Delirium has been significantly associated with a more rapid cognitive and functional decline in older adults (15–17). Further, those with delirium often have a higher future occurrence of depression and posttraumatic stress disorder (18–20).

Since delirium is associated with a higher burden of cognitive decline, depression, and posttraumatic stress disorder, there may be an increased healthcare utilization of outpatient services such as mental health, psychologists, neurologists, occupational health, and cognitive therapies. These associations need further investigation.

Strengths of this study include a demographically diverse sample with approximately 50% of the population identifying as African-American. In addition, the original randomized controlled trial that collected these data points conducted rigorous delirium severity assessments. These findings are limited as it is a secondary analysis of randomized controlled trial data, and findings are not generalizable to a population outside of critical care. The healthcare utilization data were limited to ED use and hospitalizations and did not include outpatient data such as mental health service use and neurologic service consultation. Further, this analysis is likely biased by those who experienced study attrition due to death at discharge (n = 67) from the original hospitalization and those excluded because 2-year data were unavailable from one institution (n = 33).

CONCLUSIONS

This secondary analysis did not identify a significant relationship between delirium severity trajectories and 2-year healthcare utilization and morality data. Future studies may consider how delirium influences chronic comorbidity burden and if delirium is associated with a higher use of outpatient healthcare resources, such as mental health and therapy services.

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1 *Division of Nursing Research, Department of Nursing, Mayo Clinic, Rochester, MN.*

2 *Center for Health Innovation and Implementation Science, School of Medicine, Indianapolis, IN.*

3 *Center for Aging Research, Indiana University, School of Medicine, Regenstrief Institute, Indianapolis, IN.*

4 *Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.*

5 *Division of Acute Care Surgery, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.*

6 *Sidney & Lois Eskenazi Hospital, Smith Level One Trauma Center, Indianapolis, IN.*

7 *Department of Biostatistics, Indiana University School of Medicine, Indianapolis, IN.*

8 *Division of Pulmonary, Critical Care, Sleep and Occupational Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN.*

9 *Sandra Eskenazi Center for Brain Care Innovation, Indianapolis, IN.*

10 *Department of Medicine, Indiana University School of Medicine, Indianapolis, IN.*

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For information regarding this article, E-mail: Lindroth.heidi@mayo.edu

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