Days of Delirium Are Associated with 1-Year Mortality in an Older Intensive Care Unit Population

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***Rationale*: Delirium is a frequent occurrence in older intensive care unit (ICU) patients, but the importance of the duration of delirium in contributing to adverse long-term outcomes is unclear.**

***Objectives*: To examine the association of the number of days of ICU delirium with mortality in an older patient population.**

***Methods*: We performed a prospective cohort study in a 14-bed ICU in an urban acute care hospital. The patient population comprised 304 consecutive admissions 60 years of age and older.**

***Measurements and Main Results*: The main outcome was 1-year mortality after ICU admission. Patients were assessed daily for delirium with the Confusion Assessment Method for the ICU and a validated chart review method. The median duration of ICU delirium was 3 days (range, 1–46 d). During the follow-up period, 153 (50%) patients died. After adjusting for relevant covariates, including age, severity of illness, comorbid conditions, psychoactive medication use, and baseline cognitive and functional status, the number of days of ICU delirium was significantly associated with time to death within 1 year post-ICU admission (hazard ratio, 1.10; 95% confidence interval, 1.02–1.18).**

***Conclusions*: Number of days of ICU delirium was associated with higher 1-year mortality after adjustment for relevant covariates in an older ICU population. Investigations should be undertaken to reduce the number of days of ICU delirium and to study the impact of this reduction on important health outcomes, including mortality and functional and cognitive status.**

Keywords: delirium; aging; mortality; intensive care

Delirium in the intensive care unit (ICU) is a common condition for hospitalized older patients due to the severity of their illnesses, the number of their comorbidities, and their advanced age (1–3). The development of delirium has been associated with higher morbidity, persistent functional decline, longer hospital stays, and increased costs (4–9). Previous studies have shown delirium to be associated with increased mortality (6, 10–12). Although numerous studies have documented an increased risk of mortality associated with the occurrence of delirium, to our knowledge, no investigations have focused on the effect of the number days of ICU delirium on mortality. Examining the impact of days of delirium as opposed to just the presence of delirium is particularly relevant in an ICU setting. Our prior research has demonstrated that the majority of patients present with delirium or develop delerium within the first 48 hours (3), thus making prevention of delirium challenging. Demonstrating that the number of days of delirium is an important marker of adverse outcomes will lead clinicians and investigators to examine ways to reduce days of delirium. The objective of this study was to examine the association between number of days of ICU delirium and mortality after adjusting for important comorbidities and other covariates among older ICU patients.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Older patients with critical illness are at risk for delirium, which can affect morbidity and mortality.

What This Study Adds to the Field

The number of days of delirium older patients experience during an intensive care unit admission is significantly associated with mortality up to 1 year after admission after controlling for severity of illness. These findings make it imperative to find ways to reduce duration of delirium in the intensive care unit.

METHODS

The study participants were 304 consecutive patients 60 years of age or older who were admitted to the medical ICU at Yale-New Haven Hospital from September 5, 2002, through September 2004. Figure 1 presents the enrollment data for the study participants. Informed consent for participation was obtained from proxy respondents according to procedures approved by the Institutional Review Board of Yale University School of Medicine. Patients were critically ill; therefore, proxy respondents were also used as the primary source of baseline information as previously described (13, 14). Medical records were reviewed to obtain information about demographic characteristics, admitting diagnoses, acute and chronic health conditions, and medication usage.

Main Predictor Variable

The main predictor was the number of days of ICU delirium recorded as a time-varying covariate. Delirium was assessed Monday through Friday during the ICU stay using the Confusion Assessment Method ICU (CAM-ICU). The CAM-ICU was developed for use in critically ill, intubated patients, and details can be found at www.icudelirium.org. The CAM-ICU is a validated delirium detection tool with a sensitivity of 93 to 100% and a specificity of 98 to 100% and high interrater reliability (kappa = 0.96) (11, 15, 16). Alertness was measured using the Richmond Agitation Sedation Scale (17, 18). If patients had evidence of stupor/coma, the CAM-ICU was not performed. If they had stupor/coma or were unavailable, the research nurse made three more attempts during the day to obtain the CAM-ICU. Chart review was used to detect delirium on Saturday and Sunday (19, 20). The whole medical record was reviewed daily for evidence of delirium using a validated chart review method (19, 20). The CAM-ICU algorithm was used to determine delirium status (16). When the CAM-ICU was

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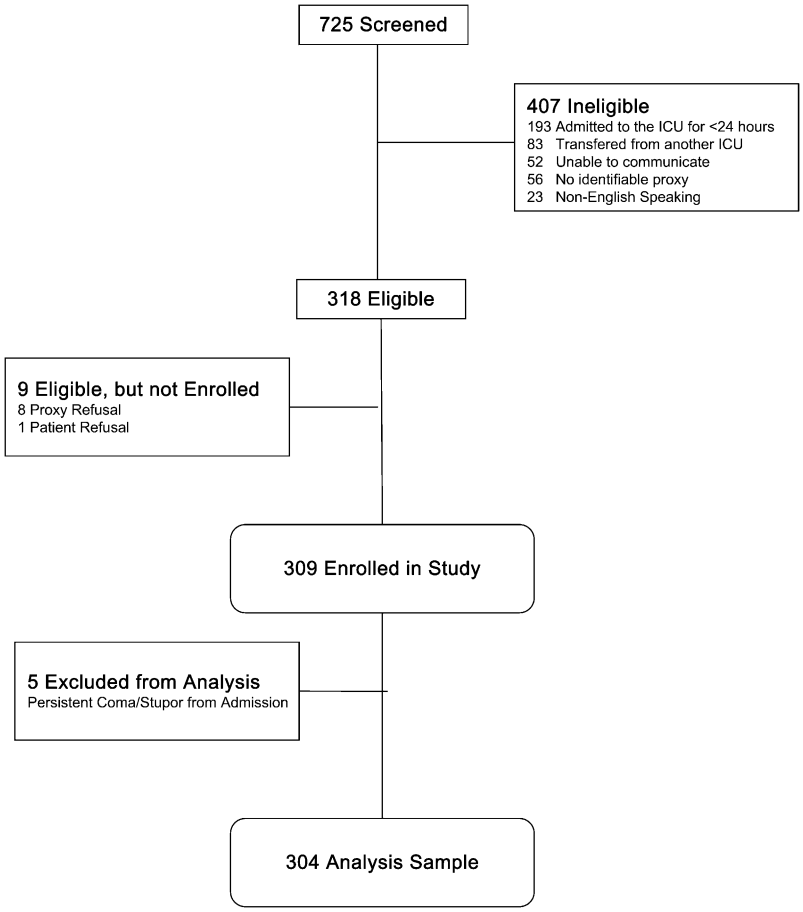

Figure 1. Patient enrollment screening and eligibility flow diagram.

unavailable, the chart review was used. If delirium occurred at any point during the 24-hour period, the day was considered a day "with delirium." Research nurses, who underwent training and interrater reliability testing for all key measures prior to study onset and at 6-month intervals, conducted study assessments. Interrater reliability was 100% between our two research nurses. The number of days of ICU delirium was calculated from the ICU admission date through ICU discharge. For participants who required readmission to the ICU within a few days of their initial discharge, days of delirium occurring during their ward stay were included in the total count of days of ICU delirium.

Of special interest is our interpretation of the relationship between delirium and coma/stupor. Papadopoulos discusses septic encephalopathy with delirium occurring within a pathological spectrum ranging from normal to coma/stupor (21). We follow the argument of Papadopoulos and note there is also evidence that the majority of patients progress from coma/stupor to delirium before returning to "normal" (2). For this reason, we have included the coma/stupor days in our count of days of delirium in the ICU (i.e., our main predictor variable).

Outcome Variable

The main outcome measure for this study was time to death during the ICU stay or within the first year after ICU admission. Time to death was calculated as the number of days from ICU admission that the person survived. Observations for the time-to-death variable were censored when study participants withdrew from the study or were alive at 1 year after ICU admission.

Covariates

Control variables were determined *a priori* based on prior literature and clinical experience. Preexisting dementia was evaluated using the Informant Questionnaire on Cognitive Decline in the Elderly (13, 22). Prior studies using this instrument have demonstrated its validity compared with cognitive testing of patients (23, 24), and we have previously documented its usefulness in ICU patients (13). Dementia was defined as an Informant Questionnaire on Cognitive Decline in the Elderly score > 3.3; this cutpoint achieves a balance between sensitivity and specificity for detecting dementia (13, 24, 25). Baseline function was assessed with the Katz Activities of Daily Living Scale and higher-level function with Lawton's Instrumental Activities of Daily Living Scale (IADL) (26, 27). Other covariates included the Charlson Comorbidity Index score (28), medications on ICU admission and during the ICU stay, the Acute Physiology and Chronic Health Evaluation II score, (a measure of severity of illness [29]), and whether the patient was admitted to the ICU from the emergency room. Based on our prior work, we included the receipt of an opioid or benzodiazepine or any receipt of haloperidol during the ICU stay as control variables (30). We did not include receipt of propofol because only 7% of our patients received this medication.

Statistical Analysis

Descriptive statistics were ascertained as appropriate. An unadjusted analysis of the association between a five-level categorical version of the days of ICU delirium variable and the days of survival was conducted by creating Kaplan-Meier survival curves (31). For multivariable modeling, we used a Cox survival model (32) that included the number of days of ICU delirium main predictor and the length of ICU stay as cumulative time-varying covariates. Control variables for the multivariable model were selected on clinical grounds and were forced into the multivariable model. Covariates were represented as continuous or count variables only if they had a generally linear relationship to the mortality outcome. If clinical control variables were highly correlated (correlation coefficient >0.40), we used only the variable having the strongest association with the mortality outcome. Model fit was assessed using residual analysis and goodness-of-fit statistics. Bootstrapping was used to assess the reproducibility of the results for the main predictor of the multivariable model.

TABLE 1. PARTICIPANT CHARACTERISTICS (N = 304)

Age in years, mean ± SD	74.7 ± 8.5
Male gender, n (%)	143 (47)
Nonwhite race, n (%)	50 (16)
Dementia, n (%)	94 (31)
Direct admission to ICU from emergency room, n (%)	203 (67)
Admission to ICU from floor, n (%)	94 (31)
Admitted to the ICU within 24 h of hospital admission, n (%)	33/94 (35)
Days between hospital and ICU admission, median (range)	3 (1–38)
Admission to ICU from other (rehab), n (%)	7 (2)
Any impairment in activities of daily living, n (%)	110 (36)
Impairment in activities of daily living, median (IQR)	0.0 (1)
Any impairment in instrumental activities of daily living, n (%)	260 (86)
Impairment in instrumental activities of daily living, median (IQR)	3 (3)
Charlson comorbidity index, mean ± SD	1.8 ± 1.9
ICU admitting diagnosis: respiratory disorder, n (%)	153 (50)
APACHE II score minus Glasgow coma component, mean ± SD	21.9 ± 5.7
Intubation, n (%)	163 (54)
Receipt of opiods or benzodiazepines in the ICU, n (%)	248 (82)
Receipt of propofol in the ICU, n (%)	22 (7)
Receipt of haloperidol in the ICU, n (%)	99 (33)
ICU length of stay, median (IQR)	5.0 (6)
Total length hospital stay, median (IQR)	11.0 (12)
ICU delirium days, median (IQR)	3.0 (6)
ICU and floor/ward delirium days, median (IQR)	4.0 (9)
Post-ICU discharge, floor/ward delirium days, median (IQR)	1.0 (3)
Death in the ICU, n (%)	48 (16)
Death within 1 yr of ICU admission, n (%)	153 (50)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = Intensive Care Unit; IQR = interquartile range.

* There are missing data for four subjects (dementia, n = 3; Charlson, n = 1).

Missing values on predictor and control variables were minimal (Table 1), so a complete case analysis was conducted. A P value of 0.05 was considered to be significant for all two-sided statistical tests. SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC), was used.

RESULTS

The baseline characteristics of patients in the study sample are reported in Table 1. During the course of the 1-year follow-up, 153 (50%) patients died. Of the total 153 who died, 48 (16% of the total cohort) died during their ICU stay. Fourteen patients were withdrawn from the study, 13 due to transfer to another ICU and 1 due to the family's request. One participant did not complete the 1-year follow-up. All of these patients were censored. The median length of ICU stay was 5 days (range, 1–57 d), and the median duration of ICU delirium was 3 days (range, 0–46 d).

Kaplan-Meier survival curves were calculated using the five-level days of ICU delirium variable. Results for the log-rank statistic were highly significant, though the curves for the fourth and fifth levels were very similar (Figure 2).

Table 2 reports the multivariable Cox survival model results. The association between the number of days of ICU delirium and mortality was statistically significant (hazard ratio [HR], 1.10; 95% confidence interval [CI], 1.02–1.18) after adjusting for covariates. Multivariable model results remain the same when the model is pruned of nonsignificant ($P > 0.10$) clinical covariates (HR, 1.10; 95% CI, 1.03–1.18). As a measure of reproducibility, bootstrapping confirmed the magnitude of the parameter estimate for the model's main predictor.

Other factors significantly associated with mortality included age, impairment in IADL, Charlson Comorbidity Index, and severity of illness on ICU admission.

DISCUSSION

This study provides new evidence for the importance of the number of days of ICU delirium as a risk factor for mortality. Previous ICU studies have found an association with the presence of delirium and mortality (6) but not between number of days of delirium in ICU and mortality. The results of this

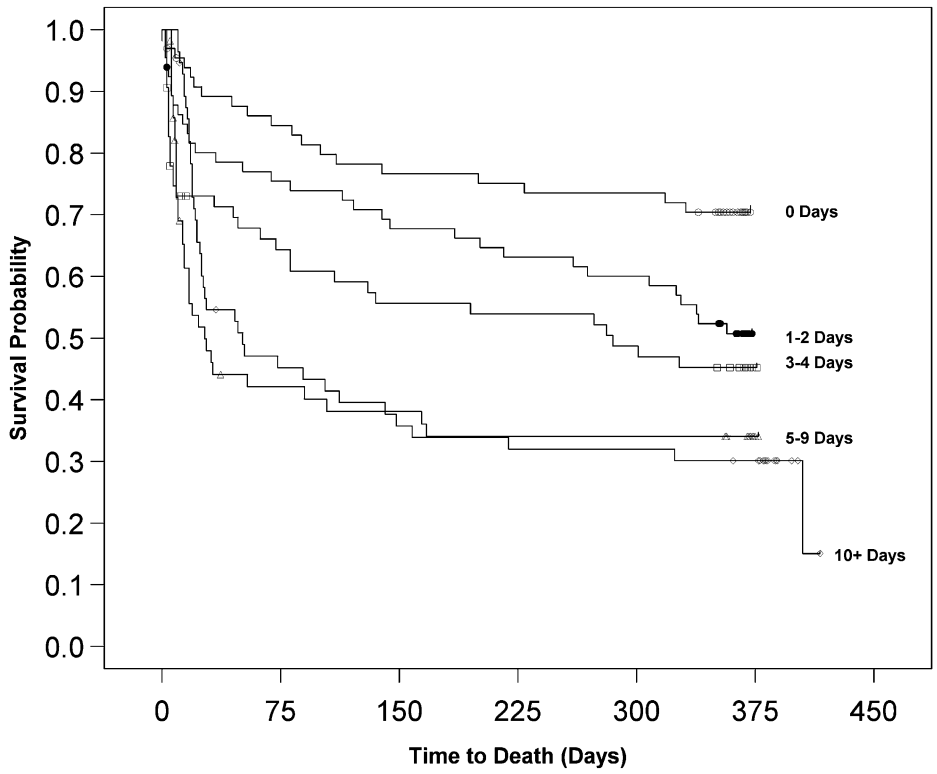

Figure 2. Kaplan-Meier survival curve for 1-year mortality post–intensive care unit (ICU) admission (ICU delirium days predictor). Log-rank chi-square statistic = 28.3; degrees of freedom = 3; $P < 001$.

TABLE 2. COX SURVIVAL MODEL: PREDICTORS OF SURVIVAL 1 YEAR AFTER INTENSIVE CARE UNIT ADMISSION (N = 300)

Variable	HR (95% CI)	*P* Value
ICU delirium days, time-varying, d	1.10 (1.02–1.18)	0.01
Age, yr	1.03 (1.01–1.05)	0.009
Male	1.33 (0.95–1.86)	0.10
Nonwhite race	0.76 (0.47–1.22)	0.26
Dementia	1.07 (0.72–1.58)	0.74
Instrumental activities of daily living (range, 0–6)	1.30 (1.16–1.45)	<0.001
Admission from emergency room	0.79 (0.55–1.13)	0.19
Charlson comorbidity index	1.21 (1.11–1.31)	<0.001
ICU admitting diagnosis: respiratory disorder	0.71 (0.48–1.05)	0.09
APACHE II score minus Glasgow Coma Component	1.05 (1.02–1.08)	0.001
Intubation	1.38 (0.83–2.30)	0.22
Receipt of opioids or benzodiazepines in the ICU	1.24 (0.70–2.19)	0.46
Receipt of haloperidol in the ICU	0.78 (0.52–1.19)	0.25
ICU length of stay, time-varying, d	0.98 (0.93–1.05)	0.59

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit.

study have important implications for the older hospitalized populations. Delirium should be considered as a significant, serious problem and treated as a possible contributor to mortality risk.

Delirium or brain dysfunction has often been thought of as a consequence of critical illness that would resolve when the acute illness resolved. Evidence is mounting that delirium itself is a strong predictor of increased length of mechanical ventilation, longer ICU stays, increased cost, prolonged neuropsychological dysfunction, and mortality (5–8, 11, 33). Our results support those shown by Ely and colleagues that ICU delirium in mechanically ventilated patients is associated with 6-month mortality (6). Lin and colleagues demonstrated increased hospital mortality in 106 mechanically ventilated patients with delirium, but there was no difference in the mean duration of ICU delirium between survivors and nonsurvivors (11). In a small cohort of mechanically ventilated patients, days of delirium were associated with persistent cognitive impairment at 3 months (34). Our work supports the findings of Ely (6) and is novel in that it demonstrates that the duration of ICU delirium is associated with mortality up to 1 year after ICU admission even after adjusting for important potential confounders. The HR of 1.10 can be interpreted as saying that "each day of delirium in the ICU increases the hazard of mortality by 10%." The cumulative effect of multiple days is multiplicative rather than additive.

Although delirium is a syndrome and there are likely multiple etiologic mechanisms that may lead to the clinical diagnosis, there is little knowledge concerning the pathogenesis of delirium in the ICU. We cannot point to a specific pathogenic process responsible for the association between delirium and increased mortality, but the pathogenic mechanisms need to be elucidated for the field to move forward.

Other factors significantly associated with 1-year mortality in our multivariable model, such as age, severity of illness, comorbidities, and impairment in IADLs, are consistent with other research on older hospitalized patients.

Although there are several studies that examine algorithms or medications for treating delirium in older hospitalized patients, these interventions have not been examined in an ICU setting (35–37). Although prevention of delirium is an ideal approach and an area of ongoing investigation, many older patients present to the ICU with delirium. In one study, 72% of the patients had delirium on their first ICU day (30). Although prevention of delirium within the ICU may be difficult, it may be possible to reduce delirium duration or severity. Schweickert and colleagues recently demonstrated a reduction in ICU delirium days with a protocol of early mobilization and occupational therapy (38).

Although treatment of the underlying critical illness is the first step in resolving delirium, there are ICU-related factors that can be addressed. One possibility that may be important in reducing delirium duration is a reexamination of the way we provide anxiety and pain control in the ICU setting. Several studies have documented the risk of delirium occurrence with the use of psychoactive medications in the ICU (3, 12, 30, 39). Recently the receipt of benzodiazepines or opioids has been associated with increased delirium duration in a cohort of older ICU patients (30). A recent randomized controlled trial demonstrated that patients who received dexmedetomidine versus midazolam for sedation had less delirium (40).

The impact of reducing delirium duration on outcomes needs to be investigated further. Though current Critical Care and Psychiatric society guidelines recommend using antipsychotics to treat delirium, there are limited data to support these recommendations (41–44). Although antipsychotics, such as haloperidol, are often given to treat delirium, especially agitated delirium, there are no randomized controlled trials of delirium treatment in critical illness, and there are no FDA-approved medications for delirium treatment. If the number of days of ICU delirium is increasing mortality up to 1 year after ICU admission, prevention and treatment strategies need to be developed.

ICU admissions are an expensive component of healthcare, accounting for 1% of the US gross domestic product annually (45). In a study by Milbrandt, after controlling for potentially confounding variables, mechanically ventilated patients with one episode of delirium had a 40% increase in ICU and total hospital costs compared with patients with no delirium (8). In this study, the presence of delirium and severity, as measured by number of days of delirium, were independently associated with increased ICU and hospital costs. In addition to a possible mortality reduction, reducing cost is an important reason to investigate strategies aimed at reducing delirium duration.

A major strength of this study is the accurate delirium detection using validated methods that included CAM-ICU and chart review for delirium. A second strength is the very high participation rate and the small amount of missing data. There are several limitations in this study. First, this was a single-site study, and although the study cohort reflected a broad range of diagnoses, other types of critically ill patients should be investigated for mortality risk from chronic delirium, including patients in surgical ICUs. Second, there are limitations associated with the definition of duration of ICU delirium. The count of the number of days of ICU delirium might have been attenuated by deaths in the ICU or by discharge from the ICU. However, we investigated the possible impact of these limitations with sensitivity analyses and bootstrapping techniques, and these supplementary findings were consistent with our reported multivariable model results.

As we begin to confront a rapidly aging society, adequate high-quality disease management and care is needed. Given that a larger number of days of ICU delirium are associated with higher mortality, increased efforts to prevent, detect, and treat delirium are needed. Without appropriate preventive and management strategies for delirium, the burgeoning older population will face an increased burden of delirium and even higher mortality.

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