Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients*

Yahya Shehabi, FCICM, EMBA; Richard R. Riker, MD; Paula M. Bokesch, MD; Wayne Wisemandle, MA; Ayumi Shintani, PhD, MPH; E. Wesley Ely, MD, MPH; for the SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group

Objectives: **To determine the relationship between the number of delirium days experienced by intensive care patients and mortality, ventilation time, and intensive care unit stay.**

Design: **Prospective cohort analysis.**

Setting: **Patients from 68 intensive care units in five countries.**

Patients: **Three hundred fifty-four medical and surgical intensive care patients enrolled in the SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) trial received a sedative study drug and completed at least one delirium assessment.**

Interventions: **Sedative drug interruption and/or titration to maintain light sedation with daily arousal and delirium assessments up to 30 days of mechanical ventilation.**

Measurements and Main Results: **The primary outcome was all-cause 30-day mortality. Multivariable analysis using Cox regression incorporating delirium duration as a time-dependent variable and adjusting for eight relevant baseline covariates was conducted to quantify the relationship between number of delirium days and the three main outcomes. Overall, delirium was diagnosed in 228 of 354 patients (64.4%). Mortality was significantly lower in patients without delirium compared to those with delirium (15 of 126 [11.9%] vs. 69 of 228 [30.3%]; $p < .001$). Similarly, the median time to extubation and intensive care unit discharge were significantly shorter among nondelirious patients (3.6 vs. 10.7 days [$p < .001$] and 4 vs. 16 days [$p < .001$], respectively). In multivariable analysis, the duration of delirium exhibited a nonlinear relationship with mortality ($p = .02$), with the strongest association observed in the early days of delirium. In comparison to 0 days of delirium, an independent dose-response increase in mortality was observed, which increased from 1 day of delirium (hazard ratio, 1.70; 95% confidence interval, 1.27–2.29; $p < .001$), 2 days of delirium (hazard ratio, 2.69; confidence interval, 1.58–4.57; $p < .001$), and ≥3 days of delirium (hazard ratio, 3.37; confidence interval, 1.92–7.23; $p < .001$). Similar independent relationships were observed between delirium duration and ventilation time and intensive care length of stay.**

Conclusions: **In ventilated and lightly sedated intensive care unit patients, the duration of delirium was the strongest independent predictor of death, ventilation time, and intensive care unit stay after adjusting for relevant covariates. (Crit Care Med 2010; 38:2311–2318)**

Key Words: delirium; mortality; mechanical ventilation; delirium duration; sedation; critically ill

Delirium is a recognized organ dysfunction complicating critical illness and constitutes a major challenge to intensive care practitioners worldwide (1–3). In a survey of critical care clinicians, >85% of responders perceived intensive care unit (ICU) delirium as a significant factor in prolonged ventilation, occurrence of hospital-acquired pneumonia, and increased hospital length of stay (4). The prevalence of delirium has been reported as high as 60%–80% in mechanically ventilated ICU patients (5–9) and 20%–50% in nonventilated ICU patients (10, 11).

***See also p. 2413.**

From the University of New South Wales Clinical School (YS), The Prince of Wales Hospital Campus, Randwick, New South Wales, Australia; University of Vermont College of Medicine (RRR), Burlington, VT, and Maine Medical Center, Portland, ME; Cubist Pharmaceuticals (PMB), Lexington, MA; Hospira (WW), Lake Forest, IL; Department of Biostatistics (AS), Vanderbilt University, Nashville, TN; Department of Medicine (SEW), Division of Pulmonary and Critical Care, Vanderbilt University, Nashville, TN, and Veteran's Affairs Geriatric Research Education Clinical Center for the Tennessee Valley Healthcare System VA, the VA GRECC, Nashville, TN.

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Study concept and design: Drs. Shehabi, Riker, Ely, and Bokesch and Mr. Wisemandle. Acquisition of data: Drs. Shehabi and Riker. Analysis and interpretation of data: Drs. Shehabi, Riker, Ely, and Shintani. Drafting of the manuscript: Drs. Shehabi, Riker, Bokesch, and Ely. Critical revision of the manuscript for important intellectual content: Drs. Shehabi, Riker, and Bokesch, Mr. Wisemandle, and Drs. Shintani and Ely. Statistical analysis: Dr. Shintani. Dr. Shintani had access to all the data used in the study and performed a full and independent analysis of all primary and secondary end points reported in this article. The results of Dr. Shintani's analysis are reported in this article.

Dr. Shehabi consulted for Hospira, Fisher-Paykel, Theravance; received honoraria/speaking fees from Hospira, Edward Lifesciences, Fisher-Paykel, and Eli-Lilly; and has received grant support from the Intensive Foundation, Melborne, Australia. Dr. Riker receives funding from Hospira. Dr. Bokesch is a past employee (as of May 2009) and has received honoraria/speaking fees from Hospira. Dr. Wisemandle is employed by Hospira, Inc, Chicago; and receives funding and has stock options from Hospira. Dr. Ely has consulted for, received grant support, and received speaking fees/honoraria from Pfizer, Hospira, GSK, and Aspect. Dr. Shintani has not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: y.shehabi@unsw.edu.au

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The impact of delirium extends beyond in-hospital illness (12), with evidence of prolonged neurocognitive impairment persisting after hospital discharge (13–15), higher rates of disposition to long-term care facilities (16) and poor functional status, and decreased quality of life (17, 18). These effects are more profound and last longer in the elderly after discharge from the ICU (19). Although the societal cost of delirium is difficult to assess, an episode of hospital or intensive care delirium has been associated with a >40% increase in healthcare costs (20). Most of the increased costs associated with ICU delirium are generated by increased ventilation and ICU time, pharmacy costs, and increased hospital-acquired complications (21).

Now recognized as a major public health problem, ICU delirium may be precipitated by modifiable risk factors (especially in critical care settings), including nonpharmacologic factors such as isolation, use of physical restraints, loss of circadian clues such as daylight, and pharmacologic factors such as choice or quantity of sedative medications (3, 22). Given that the acquisition of delirium might be prevented or its duration might be reduced, this patient-related outcome could become an ideal quality indicator if its relationship with important outcomes is further quantified (23). The financial burden of delirium provides an additional strong impetus for its prevention and mitigation (20).

Delirium has been shown to be a strong, independent predictor of mortality and prolonged hospital stay (24–26) in medical ICU patients (including some with sedative-induced coma). Recent data confirmed the benefits of light sedation and the adverse effects of drug-induced coma (27, 28). It is important now to assess whether delirium and delirium duration remain significant independent predictors of poor outcome, even among patients consistently managed without deep sedation or coma.

The aim of this cohort study was to quantify the relationship between the number of delirium days and important clinical outcomes including mortality, time on mechanical ventilation, and ICU length of stay. Unique to this cohort (7) is the protocol-mandated absence of coma both at enrollment and throughout the study, including frequent sedative titration and interruption (when needed) and daily delirium assessment.

MATERIALS AND METHODS

Study Design

Patients included in this prospective cohort analysis were recruited as part of a multicenter, randomized, controlled trial comparing dexmedetomidine and midazolam (7) conducted in ICUs at 68 medical centers in five countries between March 2005 and August 2007. The protocol was approved by the Institutional Review Board of the study centers, and all patients or legally authorized representatives provided written informed consent. Ventilated patients in participating centers were screened for inclusion/exclusion criteria. The two study sedatives, dexmedetomidine and midazolam, were continuously infused until extubation or to a maximum of 30 days to maintain a target Richmond Agitation-Sedation Scale (RASS) (29) score of −2 to +1. Sedative titration and interruption were performed as necessary. The Confusion Assessment Method for the ICU (5) was conducted daily until 48 hrs after cessation of the study drug. This cohort analysis was based on the occurrence or absence of delirium during the treatment period, regardless of sedative drug group assignment. Although data related to study drug assignment have been published (7), these clinical outcomes (including mortality, time on mechanical ventilation, and ICU length of stay) have not been evaluated relative to the occurrence and duration of delirium.

Patients

The patients in this cohort were derived from the previously published SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) trial (7). The *a priori*-defined inclusion criteria required at least one delirium assessment (the independent variable) during treatment at any time throughout the study period. A total of 354 patients who were ventilated and received a study drug met that cohort definition (Fig. 1). All patients were within the RASS score range of −2 to +1 at enrollment and throughout the treatment by titrating or interrupting sedative medications every 4 hrs and as needed.

Exclusion criteria included trauma or burns, dialysis of any type, pregnancy or lactation, neuromuscular blockade other than for intubation, regional analgesia, general anesthesia 24 hrs before or planned after the start of study drug infusion, serious central nervous system pathology, acute hepatitis or severe liver disease, and cardiovascular instability (acute coronary ischemia, left ventricular ejection fraction of <30%, bradycardia, or hypotension despite two vasopressor infusions).

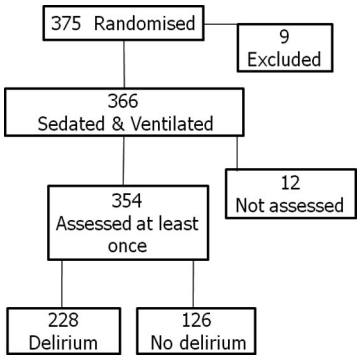

Figure 1. Patient flow diagram. Three hundred seventy-five patients were randomized in the original study (7), of whom 366 ventilated patients received a sedative infusion. Of these, 354 patients completed at least one delirium assessment during the study period and were included in the primary analysis, of whom 228 (64.4%) had delirium during the study period.

Definitions and Baseline Data Collection

Trained study personnel performed clinical evaluations daily using two well-validated instruments. The level of arousal was assessed using the RASS (29) every 4 hrs, and patients were considered in coma if the RASS score was <−3. Delirium was assessed using the Confusion Assessment Method for the ICU (5) daily from enrollment until 48 hrs after extubation or cessation of sedative medication as per protocol. Patients were considered delirious if they had a positive Confusion Assessment Method for the ICU result and were considered delirium-free if they were alive with a negative Confusion Assessment Method for the ICU result. Baseline demographics, presenting diagnostic category, Acute Physiology and Chronic Health Evaluation II score (30), relevant hemodynamic, biochemical, and hematologic data, and detailed information regarding previous sedation and concurrent medications were also collected.

Statistical Analysis

The primary analysis was based on all subjects who were randomized and received either dexmedetomidine or midazolam and had at least one delirium assessment during treatment. Baseline characteristics were described using mean and standard deviation (SD) for continuous variables, and frequency and percentage were used for categorical variables.

The primary outcome for this cohort analysis was all-cause 30-day mortality defined as death occurring up to 30 days after the start of the study drug. Secondary outcomes included the time to the first successful extubation (defined as no reintubation or death within 48 hrs after extubation) and the time to ICU dis-

charge (ICU length of stay) defined from the start of the study drug to the time of ICU transfer order. The time to event analysis was used for all outcomes. The time to death was defined from the start of the study drug to the time of death within 30 days. For 30-day mortality analysis, all patients were followed up until 30 days from the start of the study drug; thus, censoring occurred at 30 days from the start of the study drug. For ICU length of stay and time to extubation, patients were censored at 30 days from the start of the study drug when the time of ICU discharge or extubation was unknown (transfer to another institution, state, country).

The primary exposure variable was the duration of delirium, defined as the cumulative number of days that patients were observed to have delirium, which was assessed at least once per day during treatment and during 48-hr follow-up. Delirium occurring at enrollment before study drug administration was included as a baseline covariate and was not included in the duration of delirium variable. We separated baseline delirium from the main exposure component so that we were able to assess the acquisition and duration of delirium during a controlled sedation protocol with a constant light sedation target and consistent delirium assessment in all patients. The duration of delirium (in days) was analyzed as a "time-varying" exposure variable in the time-to-event analysis. With the time-dependent delirium duration (in days) variable, all patients, including those who were delirious at enrollment, were coded as delirium negative until their first on-treatment positive delirium assessment (31), and then 1 day was incrementally added when each additional delirium day occurred. For example, a patient who is delirious on day 1, normal on days 2 and 3, and then delirious on day 4 will have a score of 2 days of delirium. Therefore, time-varying analysis appropriately estimates the effect of delirium on mortality and ICU length of stay by avoiding immortal time bias (31).

We analyzed delirium using both a binary time-varying approach for Kaplan-Meier graphs and relevant clinical outcomes (see Table 2) and a nonlinear modeling approach allowing incorporation of the "dose" of delirium (i.e., delirium duration) for the multivariable analysis (see Table 3). The primary analysis for these time-to-event outcomes was a time-varying Cox proportional hazards multivariable regression model with the following eight baseline covariates chosen *a priori* because of their clinical relevance: age, baseline Acute Physiology and Chronic Health Evaluation II score, treatment assignment (dexmedetomidine, midazolam), type of ICU unit (surgical, medical), severe sepsis (yes, no), shock (yes, no), pneumonia (yes, no), and baseline delirium (yes, no).

Table 1. Patient demographics and clinical characteristics

Characteristic	Primary Cohort (%) (n = 354)
Age, mean (SD), yrs	62.0 (15.4)
Male, n (%)	177 (50.0)
Weight, mean (SD), kg	88.8 (32.3)
Acute Physiology and Chronic Health Evaluation II score,[a] mean (SD)	18.7 (6.7)
Medical ICU patients, n (%)	304 (85.9)
Surgical ICU patients, n (%)	50 (14.1)
Severe sepsis,[b] n (%)	266 (75.1)
Shock,[c] n (%)	117 (33.1)
Pneumonia, n (%)	225 (63.6)
Pre-enrollment sedative,[d] n (%)	
Benzodiazepines	283 (79.9)
Propofol	175 (49.4)
Haloperidol	24 (6.8)
Dexmedetomidine	3 (0.8)
Time from ICU admission to enrolment Median (interquartile range) hrs	39.9 (23.3–65.3)
Delirium-positive,[e] n (%)	203 (60.1)

ICU, intensive care unit; SD, standard deviation.

[a]Acute Physiology and Chronic Health Evaluation II scores not calculated at time of ICU admission but rather recorded at study enrollment using worst values over previous 24 hrs from time of study enrollment (average 40 hrs after ICU admission); [b]severe sepsis was defined as known or suspected infection with two or more systemic inflammatory response syndrome criteria and at least one new organ system dysfunction (50); [c]shock was defined as those patients whose blood pressure was being maintained via infusions of dopamine, dobutamine, norepinephrine, epinephrine, or vasopressin before start of study drug; [d]more than one sedative may have been used for a given patient; therefore, these values add up to >100%; [e]as per first delirium assessment at enrollment (n = 338) using the Confusion Assessment Method for the Intensive Care Unit, Acute Physiology and Chronic Health Evaluation II (30); Confusion Assessment Method for the Intensive Care Unit (5).

To assess if the relationship between the duration of delirium (in 1-day increments) and the outcome was constant over time as the duration increased (i.e., linear), we assessed for nonlinear association between days of delirium and outcomes (32). If the test of nonlinear effect did not reach statistical significance, then the association was presumed linear or constant.

Hazard ratios (HRs) for the specific outcomes based on the duration of delirium were computed using Cox regression with nonlinear effect of delirium by contrasting point estimates of hazard risk at 1 day, 2 days, and ≥3 days vs. 0 days of delirium. Similar multivariable analysis was conducted separately within patients with or without pre-enrollment delirium to assess differential effects of delirium duration on outcomes. A cross-product term between delirium duration and pre-enrollment delirium was included in Cox regression for statistical significance of the effect modification (i.e., interaction).

The time-varying Kaplan-Meier curves were obtained using the method described by Simon and Makuch (33), along with a significance test using Mantel and Byar estimators (34). Cumulative probability of 30-day mortality and median days to ICU discharge and to extubation were computed based on time-varying Kaplan-Meier curves between patients with and without delirium. *p* values comparing median time to ICU discharge and time to extubation were generated through Cox regression with adjustment for the same set of eight covariates described. All data analyses were performed using SAS 9.1 (SAS Institute, Cary, NC) and R version 2.9.0 (http://www.r-project.org). A two-sided significance level of .05 was used for all statistical inferences.

RESULTS

Cohort Demographics at Baseline

The study schematic is presented in Figure 1. Nine patients were excluded after randomization when inclusion/exclusion criteria were recognized. Among the remaining 366 lightly sedated and mechanically ventilated patients, 354 patients had delirium assessed at least once during the treatment period, meeting the *a priori*-defined inclusion criteria. The baseline characteristics are shown in Table 1. The study population was mainly medical ICU patients. Severe sepsis was the most common admitting diagnosis. Out of 338 patients who had both pre-enrollment and poststudy drug Confu-

sion Assessment Method for the ICU assessments recorded, 203 (60.1%) patients had delirium at enrollment. No patients were deeply sedated (RASS score, −3) or in coma (RASS score, −4 or −5) at the time of enrollment.

Delirium Prevalence and Clinical Outcomes

The overall prevalence of delirium during the study period was 64.4% (228 of 354 patients). The 30-day all-cause mortality of patients without delirium was 11.9% (15 of 126), compared to 30.3% (69 of 228) for those with at least 1 day of delirium ($p < .001$) (Table 2). Similar effects were observed for the median time to extubation (which was 7 days shorter in nondelirious patients; $p < .001$) and the median ICU length of stay (which was 12 days shorter in nondelirious patients; $p < .001$) (Table 2).

Delirium Duration vs. Mortality

The majority of delirious patients (80.3% [183 of 228]) experienced delirium for ≤4 days. The duration of delirium experienced by all patients is shown in Figure 2, with the cumulative number of delirium days displayed for all 228 patients experiencing delirium. A dose-response increase in mortality was seen with increasing durations of delirium from 0 to 1, 2, and ≥3 delirium days (11.9%, 14.5%, 22%, and 39%), respectively (Table 2).

The time-varying Cox proportional hazards multivariable regression model adjusting for eight baseline covariates showed delirium duration to be the strongest independent predictor of 30-day mortality (Fig. 3*A*; $p < .001$) and demonstrated a significant increase in HRs for death when delirium duration increased from 1 to 2 to ≥3 days compared with no delirium (Table 3). Age (HR, 1.25; 95% confidence interval [CI], 1.04–1.49; $p = .01$) and Acute Physiology and Chronic Health Evaluation II score (HR, 1.21; 95% CI, 1.02–1.42; $p = .02$) were of lesser significance as predictors of 30-day all-cause mortality. Sedation treatment assignment (HR, 0.76; $p = .28$), delirium at enrollment (HR, 0.84; $p = .50$), diagnosis of severe sepsis (HR, 1.55; $p = .17$), shock (HR, 0.63; $p = .08$), ICU type (HR, 0.54; $p = .12$), and pneumonia (HR, 1.29; $p = .38$) did not independently predict the risk of death at 30 days. A significant nonlinear relationship was observed between delirium duration and mortality (the p value for the overall effect of delirium days was <.001 and =.02 for the nonlinear effect). The association of delirium with mortality was most pronounced in the early days of delirium.

Table 2. Relevant clinical outcomes

Median (interquartile range) number of delirium days		
All patients (n = 354)	1 (0,3) days	
Among patients with delirium (n = 228)	3 (2,4) days	
30-day all cause mortality (% and N)		
0 days of delirium	11.9% (15 of 126)	$p < .001$[a]
Delirium (1+ days)		
1 day of delirium	14.5% (8 of 55)	
2 days of delirium	22.0% (9 of 41)	
≥3 days of delirium	39.0% (52 of 132)	
Median days to extubation[b]		
No delirium	3.6 (1.8, 5.3)	$p < .001$[a]
Any delirium	10.7 (5.8, 22.3)	
Median days to intensive care unit discharge[b]		
No delirium	4 (3, 6)	$p < .001$[a]
Delirium	16 (7, 23)	

[a]Obtained based on a Cox regression model in which delirium was quantified as binary time-varying variable (presence or absence) adjusting for age, baseline Acute Physiology and Chronic Health Evaluation II score, randomized treatment assignment (dexmedetomidine, midazolam), type of intensive care unit (surgical, medical), baseline presence of severe sepsis (yes, no), baseline presence of shock (yes, no), baseline presence of pneumonia (yes, no), and baseline presence of delirium (yes, no); [b]obtained based on time-varying Kaplan-Meier curves with delirium days as a time-dependent variable.

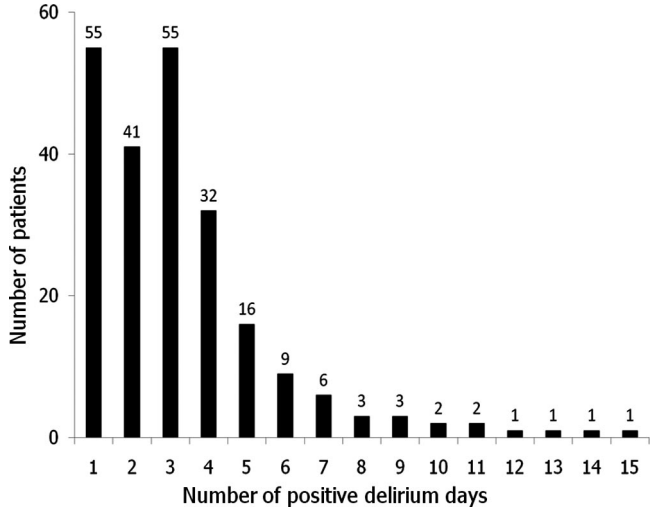

Figure 2. Number of patients vs. cumulative number of delirium days. Cumulative delirium was calculated by adding the number of delirium days experienced by each patient during the study period. The majority of patients experienced a total of ≤4 days in delirium (183 of 228 [80.3%]) and only 14 (6.1%) patients experienced delirium >7 days.

Delirium Duration vs. Time on Mechanical Ventilation

A dose-response relationship was observed between delirium duration and remaining intubated, with the HRs for 1, 2, and ≥3 delirium days found to be 1.80, 2.82, and 3.88, respectively (Table 3). The time-varying Cox proportional hazards multivariable model showed that the number of delirium days was the most significant predictor of time on mechanical ventilation (i.e., the hazard of remaining intubated) (Table 3, Fig. 3*B*). Among other baseline covariates, age (HR, 1.18; 95% CI, 1.06–1.30; $p = .02$) was also a significant predictor of time to extubation, whereas the choice of sedative agent (HR, 1.14; $p = .55$), Acute Physiology and Chronic Health Evaluation II score (HR, 1.01; $p = .91$), delirium at enrollment (HR, 0.96; $p = .84$), diagnosis of severe sepsis (HR, 1.38; $p = .19$), shock (HR, 0.87; $p = .51$), and diagnosis

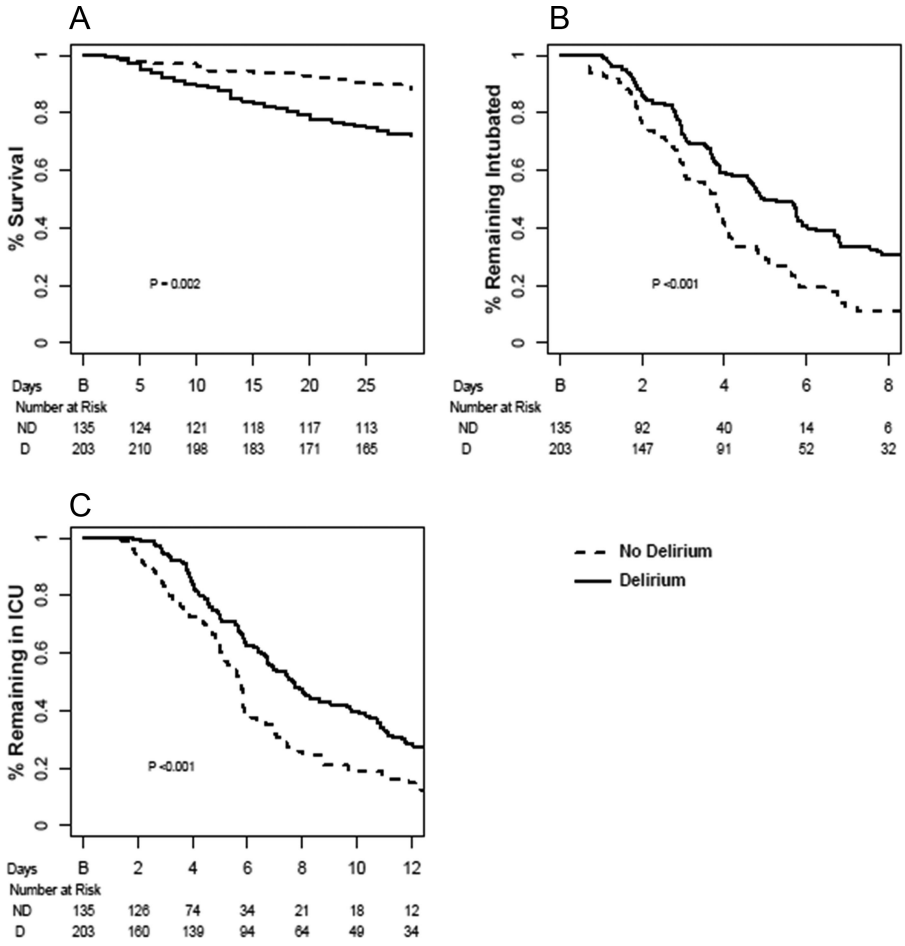

Figure 3. Kaplan-Meier graphs showing the relationship between delirium and the three main clinical outcomes. *A*, Mortality. A higher risk of death was evident in delirious patients (*solid line*) as compared to nondelirious patients (*dashed line*) during 30 days following enrollment. By day 15, the death rate in delirious patients was three times higher than in those without delirium. *B*, Time on mechanical ventilation. A higher risk of remaining intubated was observed early in delirious patients (*solid line*), was the largest separation seen at 4 days following enrollment and sustained thereafter. *C*, Intensive care unit (*ICU*) length of stay. A higher risk of remaining in the ICU occurred early in the delirious patients (*solid line*) with the largest separation seen between days 4- and 10 after enrollment. All graphical data and *p* values were determined analyzing delirium as a time-varying covariate, and statistical significance measures were determined using Cox regression with adjustment for eight covariates: age, baseline Acute Physiology and Chronic Health Evaluation II, treatment assignment, surgical vs. medical ICU, severe sepsis, pneumonia, and baseline delirium. Patients were categorized as delirium positive at the first positive delirium assessment after enrollment. Curves were constructed using Mantel and Byar estimators (35). *B*, number at risk at baseline; *D*, delirium positive; *ND*, delirium-negative. Log-rank *p* values are shown.

of pneumonia (HR, 1.22; $p = .37$) were not predictive of risk of remaining intubated. The relationship over time between delirium days and the risk of remaining intubated demonstrated a linear effect (for overall effect of delirium days, $p < .001$; for nonlinearity, $p = .20$) with each additional day of delirium.

Delirium Duration vs. ICU Length of Stay

Delirium was the strongest predictor of ICU length of stay and similarly showed a dose-response increase in the risk of remaining in ICU from 1 to 2 to ≥3 delirium days (HR, 1.21 to 1.43 to 1.61, respectively) (Table 3, Fig. 3*C*). The Cox proportional hazards multivariable model showed age to be a significant predictor of ICU stay (HR, 1.18; 95% CI, 1.06–1.30; $p = .002$), whereas delirium at enrollment (HR, 1.09; $p = .61$), Acute Physiology and Chronic Health Evaluation II score (HR, 1.08; $p = .41$), the choice of sedative agent (HR, 1.09; $p = .55$), diagnosis of severe sepsis (HR, 1.28; $p = .17$), shock (HR, 1.27; $p = .13$), and diagnosis of pneumonia (HR, 1.02; $p = .92$) did not predict the risk of remaining in ICU. The number of delirium days exhibited a linear relationship (for nonlinearity, $p = .34$) with the risk of staying in ICU (for the overall effect, $p = .02$).

Using pre-enrollment delirium, multivariable analysis showed a strong association between delirium duration (comparing 0 day vs. 3 days of delirium) and mortality (HR, 7.14 and $p < .001$ vs. HR, 2.4 and $p = .12$), ventilation time (HR, 7.69 and $p < .001$ vs. HR, 2.12 and $p = .12$), and ICU stay (HR = 2.04, $p = .003$ vs. HR = 1.16, $p = .82$). However, there was no significant interaction between

Table 3. Multivariable analysis of cumulative number of delirium days

Number of Delirium Days ($p < .001$, Overall)	30–Day Mortality ($p = .02$, Nonlinear Effect)[a]			Remaining Intubated ($p < .001$, Overall)			Remaining in Intensive Care Unit ($p = .02$, Overall)		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
0 vs. 1 day	1.70	1.27–2.29	<.001	1.80	1.27–2.55	<.001	1.21	1.00–1.47	.05
0 vs. 2 days	2.69	1.58–4.57	<.001	2.82	1.67–4.77	<.001	1.43	1.02–2.01	.04
0 vs. 3 days	3.73	1.92–7.23	<.001	3.88	2.13–7.03	<.001	1.61	1.08–2.41	.02

HR, hazard ratio; CI, confidence interval.

[a] $p > .05$ for nonlinear effect for the other outcomes (remaining intubated and remaining in intensive care unit). HRs were generated from Cox regression in which number of delirium day was modeled as a nonlinear continuous time-dependent variable adjusting for age, baseline Acute Physiology and Chronic Health Evaluation II score, randomized treatment assignment (dexmedetomidine, midazolam), type of intensive care unit (surgical, medical), baseline presence of severe sepsis (yes, no), baseline presence of shock (yes, no), baseline presence of pneumonia (yes, no), and baseline presence of delirium (yes, no). HR for the duration of delirium was computed based on the Cox regression model as a ratio of relative hazards on days 1, 2, and ≥3 to that of 0 days.

baseline delirium and mortality ($p = .11$), ventilation time ($p = .06$), or duration of ICU stay ($p = .08$).

DISCUSSION

This international, multicenter study demonstrated the profound and independent association between the duration of delirium and important clinically significant outcomes, including mortality, ventilation time, and length of ICU stay, in this cohort of lightly sedated patients. We found a dose-response increase in association with the three main outcomes. One day of delirium was associated with a 70% higher risk of death, and each additional day of delirium linked to a 100% increase in the risk of dying or remaining intubated and a 20% greater chance of remaining in the ICU independent of the eight covariates adjusted for in the multivariable analysis. These findings are the first in a large cohort of ICU patients managed with a sedation protocol that precluded medication-induced coma, suggesting that even when "lighter" sedation practices are utilized, delirium occurs frequently and is associated with worse outcomes.

The relationship between the duration of delirium and mortality was nonlinear, with a greater effect observed earlier in the course of delirium. This is of particular significance because the majority of patients experienced delirium for <4 days. These data suggest that the harm of delirium may occur early in the period of brain dysfunction for ICU patients. Clinicians may better serve their patients by routinely monitoring for delirium and aggressively working to identify and treat potential causes.

Our results concur with the conclusion of recent meta-analysis (38) showing that delirium association with poor outcome is independent of other important covariates. It also complement recent findings by Pisani et al (26) showing that the duration of delirium in older ICU patients was associated with increased mortality. However, distinct important differences must be pointed out between these two studies. Our multicenter study included only ventilated patients and excluded patients with dementia or coma. In addition, we targeted a consistent sedation practice, which is moving, in general, toward light sedation level for all patients (27, 28, 35–37). We also adjusted for baseline delirium, identified the nonlinear effect of early delirium, and utilized time-varying analysis to estimate the effect of delirium on outcomes, thereby avoiding immortal time bias (31).

This study was nested within the randomized SEDCOM trial (7), which compared the effect of light sedation with dexmedetomidine vs. midazolam. The SEDCOM study concluded that dexmedetomidine reduced the prevalence of delirium and shortened the duration of mechanical ventilation, whereas this cohort study found that the duration of delirium was associated with an increased risk of death and prolonged intubation, independent of drug treatment allocation. Although these results may appear incongruous, they provide different answers to related questions. Although dexmedetomidine and midazolam appear to differentially affect the rate of delirium, they do not alter the relationship between delirium (and its duration) and mortality or ICU length of stay. This can be understood by considering the well-described "mediator effect" (39) with reduction in ventilation time mediated by reduction in delirium. Thus, statistical methods utilized to assess the impact of delirium duration on ventilation time will significantly underestimate the effect of the sedative agents.

These findings raise important questions regarding delirium and outcome. Will reducing the duration of delirium improve outcomes such as better survival or reduced length of stay? Which of the many factors contributing to delirium and long-term cognitive dysfunction (including age, severity of illness, drug withdrawal syndromes, severe sepsis, exposure to sedative and analgesic medications, sleep deprivation, and prolonged immobilization) are most important and modifiable (40–43)? Although we do not yet have answers to these questions, medications administered during ICU treatment may be among the most modifiable of risk factors. The use of benzodiazepines, opioids, propofol, and cholinergic agents for critically ill ICU patients are associated with higher rates and longer durations of delirium in several studies (7, 11, 44, 45). Although dexmedetomidine has been shown to reduce the rate and/or the duration of delirium in some studies (7, 45), other reports were equivocal (6, 46). Well-designed and adequately powered clinical trials are needed to better answer these questions. These and other risk factors for ICU delirium represent components of ICU care (47–49) that must be studied in future clinical trials.

Several limitations of our investigation must be highlighted. Our study was nested within a randomized controlled trial that limited follow-up to 30 days and did not assess long-term neurocognitive outcomes. Furthermore, our design precluded accurate assessment of pre-enrollment delirium and its duration. Therefore, pre-enrollment drivers of delirium could not be accurately quantified or differentiated from delirium occurring after randomization. Nevertheless, the presence of delirium at the time of enrollment suggests a strong association with poor outcome. Our data were obtained within the structure of a randomized clinical trial, and different designs and populations may produce different results; to increase the strength of our conclusions, we analyzed the data several different ways, yielding consistent and highly significant results. It is possible that unmeasured and important confounders such as genetic variability or unrecognized preexisting cognitive dysfunction could affect our conclusions, although we included the most commonly recognized factors in our analysis (3, 11, 22, 41–42). Despite these limitations and in addition to the study design and sedation practice incorporated, our study has several strengths, including a robust statistical methodology that handled delirium duration as a time-dependent covariate, avoided immortal time bias, and had a large sample size, well-measured independent variable, and adequate testing for mediation and correlation effect between variables.

The link between delirium and poor outcomes appears strong. However, the causal relationship between delirium and poor outcomes needs further evaluation and quantification. The mechanism by which delirium develops and exerts its harmful effect is yet to be elucidated. A better mechanistic understanding would improve future study designs to answer these important questions.

CONCLUSION

The number of delirium days experienced by lightly sedated and mechanically ventilated patients was the strongest independent predictor of death, time on mechanical ventilation, and length of ICU stay. We confirmed that the association of delirium with relevant clinical outcomes has a dose-response effect, even after adjusting for eight relevant covariates chosen *a priori*. These data add to our understanding of

the importance of brain dysfunction (delirium), even in the absence of medication-induced coma and when important aspects of contemporary sedation management are included. This study does not prove that reducing the incidence or duration of delirium will improve outcomes, but efforts to evaluate this hypothesis, incorporating important clinical outcomes such as mortality and long-term neurocognitive dysfunction, are the logical next step.

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