

# Delirium as a predictor of long-term cognitive impairment in survivors of critical illness

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## LEARNING OBJECTIVES

After participating in this educational activity, the participant should be better able to:

1. Assess risk factors and predictors of long-term cognitive impairment following critical illness.
2. Measure presence or absence of delirium in the intensive care unit.
3. Counsel families about risk for long-term cognitive impairment in mechanically ventilated intensive care unit patients with delirium.

Unless otherwise noted below, each faculty or staff's spouse/life partner (if any) has nothing to disclose.

Dr. Girard has disclosed that he received honoraria from Hospira, Inc. Dr. Jackson has disclosed that he is currently receiving grants/research funds from the National Institutes of Health. Dr. Pandharipande has disclosed that he received honoraria from Hospira, Inc. and GlaxoSmithKline; received grants/research funds from Hospira, Inc.; and is on the speaker's bureau for France Foundation—CME organizers for Hospira Inc. Ms. Pun has disclosed that she was and is a consultant/advisor for Hospira, Inc. Dr. Ely has disclosed that he received and is currently receiving grants/research funds from Hospira, Pfizer, GlaxoSmithKline, and Aspect; was a consultant/advisor for Hospira, GlaxoSmithKline, and Aspect; was on the speaker's bureau of Hospira, Pfizer, GlaxoSmithKline, and Aspect; and is a consultant/advisor for, and on the speaker's bureau of, Hospira, Pfizer, GlaxoSmithKline, and Aspect. The remaining authors have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

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**Objective:** To test the hypothesis that duration of delirium in the intensive care unit is an independent predictor of long-term cognitive impairment after critical illness requiring mechanical ventilation.

**Design:** Prospective cohort study.

**Setting:** Medical intensive care unit in a large community hospital in the United States.

**Patients:** Mechanically ventilated medical intensive care unit patients who were assessed daily for delirium while in the intensive care unit and who underwent comprehensive cognitive assessments 3 and 12 mos after discharge.

**Measurements and Main Results:** Of 126 eligible patients, 99 survived  $\geq 3$  months after critical illness; long-term cognitive outcomes were obtained for 77 (78%) patients. Median age was 61 yrs, 51% were admitted with sepsis/acute respiratory distress syndrome, and median duration of delirium was 2 days. At 3-mo and 12-mo follow-up, 79% and 71% of survivors had cognitive impairment, respectively (with 62% and

36% being severely impaired). After adjusting for age, education, preexisting cognitive function, severity of illness, severe sepsis, and exposure to sedative medications in the intensive care unit, increasing duration of delirium was an independent predictor of worse cognitive performance—determined by averaging age-adjusted and education-adjusted T-scores from nine tests measuring seven domains of cognition—at 3-mo ( $p = .02$ ) and 12-mo follow-up ( $p = .03$ ). Duration of mechanical ventilation, alternatively, was not associated with long-term cognitive impairment ( $p = .20$  and  $.58$ ).

**Conclusions:** In this study of mechanically ventilated medical intensive care unit patients, duration of delirium (which is potentially modifiable) was independently associated with long-term cognitive impairment, a common public health problem among intensive care unit survivors. (Crit Care Med 2010; 38:1513–1520)

**KEY WORDS:** delirium; intensive care units; mechanical ventilation; cognitive impairment; aged

At the conclusion of this CME activity, participants will be able to better estimate the risk of long-term cognitive impairment in mechanically ventilated intensive care unit (ICU) patients. Although advances in critical care medicine have significantly reduced mortality for patients with critical illness, survivors often do not recover to their previous cognitive or functional status (1). As many as six out of every 10 patients who survive critical illness will struggle with significant cognitive impairment months to years after their ICU stay (2). Often manifesting functionally as an acquired dementia, long-term cognitive impairment after critical illness can greatly reduce quality of life (3, 4), increase health care costs (5), and lead to institutionalization (6). With the number of patients requiring critical care increasing dramatically each year (7), cognitive impairment after critical illness is an increasingly important major public health problem.

Although numerous studies have documented that persistent cognitive impairment affects 30% to 80% of ICU survivors (3, 8–14), a vital and unmet need in medicine is the determination of risk factors and predictors of this pernicious complication of critical illness. Without knowledge about specific risk factors, clinicians cannot take deliberate measures to prevent this potentially devastating outcome.

Delirium, an acute form of brain dysfunction affecting 60% to 80% of mechanically ventilated ICU patients (15–18), has been shown to predict cognitive decline among older patients without critical illness (19–21). In light of these non-ICU data and the known association between duration of delirium in the ICU and 1-yr mortality (22), we hypothesized that duration of delirium is an indepen-

dent predictor of long-term cognitive impairment after critical illness and that patients with prolonged ICU delirium are at highest risk for poor cognitive outcomes. To test this hypothesis, we conducted the first prospective cohort study with 1-yr follow-up to determine whether duration of delirium is a predictor of long-term cognitive impairment among mechanically ventilated medical ICU patients.

## MATERIALS AND METHODS

### Study Design and Population

This prospective cohort study was nested within the Awakening and Breathing Controlled randomized trial (ClinicalTrials.gov NCT00097630) that evaluated a paired sedation and ventilator weaning protocol for mechanically ventilated ICU patients (23). Adult medical ICU patients who were mechanically ventilated  $>12$  hrs were eligible for enrollment in the clinical trial unless they were admitted after cardiopulmonary arrest, had neurologic deficits that prevented them from living independently (e.g., severe dementia or large stroke), were moribund and/or not committed to aggressive therapy, had been ventilated continuously  $>2$  wks, or were enrolled in a trial that did not allow co-enrollment. Of patients enrolled in the trial at Saint Thomas Hospital in Nashville, Tennessee, those who survived to hospital discharge were eligible for inclusion in the current long-term cohort study unless they underwent cardiac bypass or neurosurgery during their hospitalization.

At the time of enrollment, written informed consent was obtained from authorized surrogates because patients were typically unable to provide consent; the participants themselves also provided consent before discharge from the hospital. The institutional review boards at Saint Thomas Hospital (Nashville, TN) and Vanderbilt University (Nashville, TN) approved the study protocol.

### Exposure, Covariates, and Outcomes

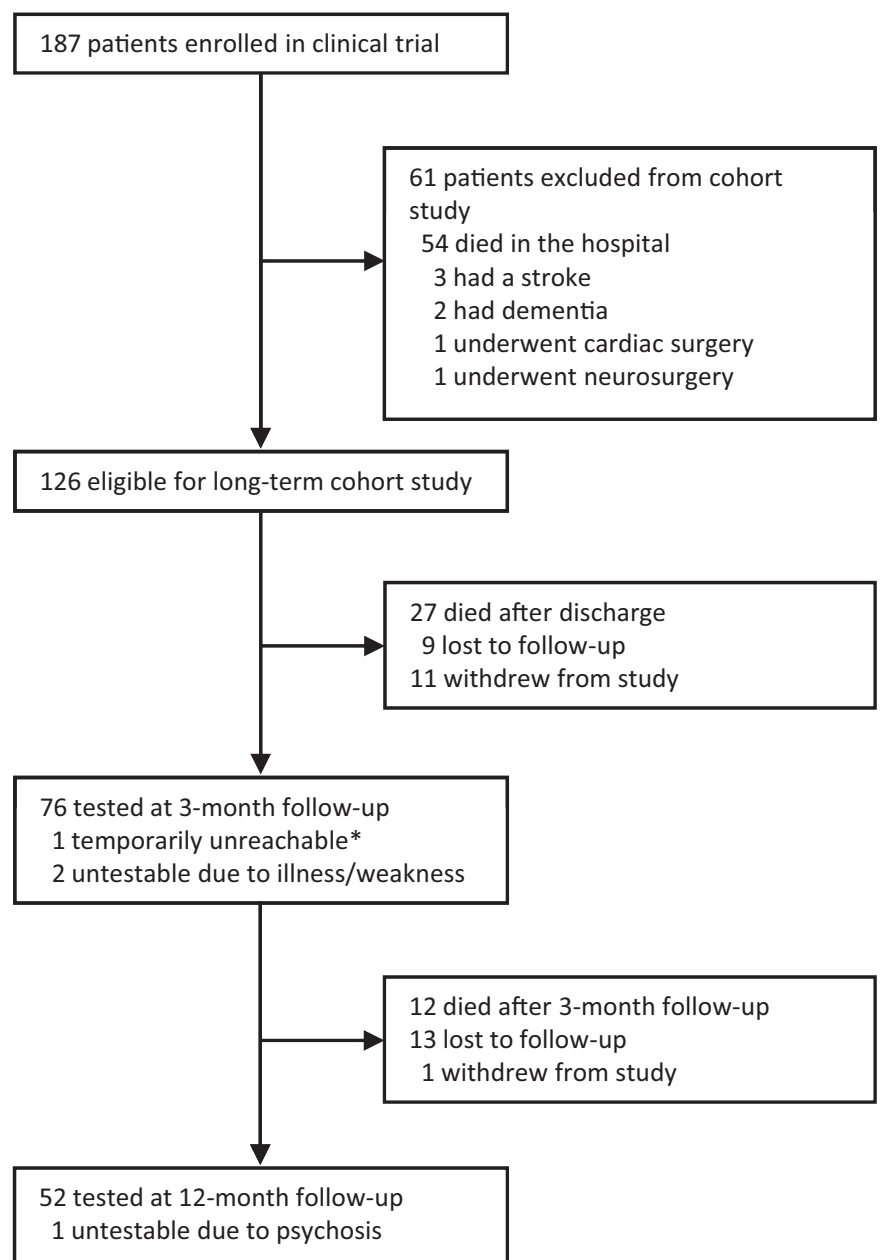
The primary exposure variable was duration of delirium in the ICU. We determined *a priori* to analyze delirium exposure in days rather than as a dichotomous variable (e.g., delirium vs. no delirium) for three reasons. First, we considered it biologically plausible that a patient with 1 day of delirium followed by recovery was more similar (regarding risk for long-term cognitive impairment) to a patient without any delirium than to a patient who remained delirious for many days. Second, previous research suggests that duration of delirium has prognostic significance because days of delirium is an independent predictor of long-term survival (15, 22). Finally, categorization of a continuous variable results in a significant loss of power and residual confounding (24).

Trained study personnel assessed patients for delirium each day until ICU discharge or for a maximum of 28 days using the Confusion Assessment Method for the ICU (CAM-ICU) (25, 26). Duration of delirium was defined as the number of days in the 28-day study period during which patients were CAM-ICU positive and were not comatose. Level of consciousness was assessed each day using the Richmond Agitation-Sedation Scale (27, 28), and coma was defined as no response to verbal or physical stimulation (Richmond Agitation-Sedation Scale, Scale  $-5$ ) or response to physical or painful stimulation but no response to voice alone (Richmond Agitation-Sedation Scale  $-4$ ).

A secondary independent exposure variable was duration of mechanical ventilation measured from the time of endotracheal intubation to the beginning of successful unassisted breathing, which started with the first extubation—or removal of ventilatory support for patients with a tracheostomy—that was followed by at least 48 consecutive hours of unassisted breathing.

Covariates, which were selected *a priori* based on clinical suspicion and biological plausibility, were collected at enrollment or during the ICU stay and included age, years of education, preexisting cognitive function, severity of illness, severe sepsis, Awakening and Breathing Controlled Trial treatment group (23), and total doses of benzodiazepines, opiates, and propofol administered in the ICU. Severe sepsis was identified according to treating physicians' diagnoses and confirmed using standard definitions (29). Each severe sepsis patient had known or suspected infection, systemic inflammatory response syndrome, and acute organ dysfunction in the form of respiratory failure necessitating invasive mechanical ventilation. Although we excluded patients with dementia severe enough to prevent them from living independently, patients with less severe cognitive impairment were eligible for enrollment. We therefore assessed preexisting cognitive function at enrollment using the Short Informant Questionnaire of Cognitive Decline in the Elderly (30, 31), a validated surrogate questionnaire. For young patients who had cognitive impairment per their surrogate's report and for all patients older than 60 yrs, we administered the Short Informant Questionnaire of Cognitive Decline in the Elderly and included their score as a continuous covariate in the multivariable models. Patients younger than 60 yrs without suspected cognitive impairment according to their surrogate's report were assigned a score of 3, indicating an absence of recent cognitive decline. Severity of illness at enrollment was measured using the acute physiology score component of the Acute Physiology and Chronic Health Evaluation II score (32).

Three and 12 mos after enrollment, cognitive outcomes were assessed in person by a neuropsychologist (JCJ) who was blinded to the details of each patient's critical illness, including delirium duration. We tested patients using a comprehensive battery of nine neuropsychological tests designed to measure seven core domains of cognitive functioning. Specifically, to assess cognitive domains we hypothesized to be likely affected by critical illness, we administered: 1) the Digit Span (33) and Trailmaking Test A (34) to assess attention and concentration; 2) Digit Symbol Coding (33) to assess information processing speed; 3) the Rey Auditory Verbal Learning Test (35) to assess verbal memory; 4) the Rey-Osterreith Complex Figure (36) (copy test and 30-min delay) to assess visual-spatial construction and delayed visual memory; 5) Trailmaking Test B (34) to assess executive functioning; 6) the Verbal Fluency Test (37) to assess language; and 7) the Mini-Mental State examination (38) to assess global mental status. Each patient's cognitive test scores were converted to T-scores using age-specific and education-specific normative data, and a summary score of cognitive performance was calculated by averaging the T-scores of all nine cognitive tests in the manner used previously (39). For descriptive purposes, we also categorized patients in keeping with previous research on cognitive outcomes (40–42). Specifically, we classified patients as having mild to moderate impairment if they had either two cognitive test scores 1.5 standard deviations (SD) below the mean or one cognitive test score 2 SD below the mean; we classified patients as having severe cognitive impairment if they had three or more cognitive test scores 1.5 SD below the mean or two or more cognitive test scores 2 SD below the mean. Patients with scores higher than 1.5 SD below the mean on all nine tests covering



**Figure 1.** Enrollment and follow-up. \*One patient who was not reached for testing at 3-mo follow-up was fully tested at 12-mo follow-up, so cognitive outcomes were obtained for a total of 77 patients at 3-mo and/or 12-mo follow-up.

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## Statistical Analysis

Baseline demographics and clinical characteristics were examined using median and interquartile range for continuous variables and proportions for categorical variables. To compare patients who were discharged alive from the hospital without complete follow-up to those who had complete follow-up, we used the chi-squared test for categorical variables and the Wilcoxon-Mann-Whitney two-sample rank-sum test for continuous variables.



Table 1. Baseline demographics and clinical characteristics<sup>a</sup>

Characteristic	Cohort, n = 77
Age, yrs	61 (47–71)
Female (n/total)	48% (37/77)
Education, yrs	12 (10–13)
Short Informant Questionnaire of Cognitive Decline in the Elderly	3.0 (3.0–3.4)
Cognitive impairment (n/total) <sup>b</sup>	9% (7/77)
Acute Physiology and Chronic Health Evaluation II	29 (23–34)
Admission diagnoses, % (n/total)	
Severe sepsis/acute respiratory distress syndrome	51% (39/77)
Myocardial infarction/congestive heart failure	20% (15/77)
Chronic obstructive pulmonary disease/asthma	8% (6/77)
Altered mental status	6% (5/77)
Hepatic or renal failure	4% (3/77)
Malignancy	1% (1/77)
Alcohol withdrawal	1% (1/77)
Other	9% (7/77)
Delirium in the intensive care unit	
Prevalence (n/total)	84% (65/77)
Duration, days	2 (1–5)
Intervention group (n/total)	57% (44/77)
Sedative exposure	
Total benzodiazepine dose, mg <sup>c</sup>	10 (1–77)
Total opiate dose, μg <sup>d</sup>	255 (0–10,270)
Total propofol dose, mg	5,600 (0–17,390)

<sup>a</sup>All results expressed as median (interquartile range) or % (n/total); <sup>b</sup>patients with a Short Informant Questionnaire of Cognitive Decline in the Elderly score  $\geq 4.0$  were considered to have mild preexisting cognitive impairment; patients with severe dementia preventing them from living independently were excluded from enrollment; <sup>c</sup>data shown in lorazepam equivalents; <sup>d</sup>data shown in fentanyl equivalents.

Table 2. Cognitive outcomes during follow-up

Outcome, % (n/Total)	Follow-up Assessment	
	3 mos (n = 76) <sup>a</sup>	12 mos (n = 52) <sup>a</sup>
No impairment	21% (16/76)	29% (15/52)
Mild/moderate impairment	17% (13/76)	35% (18/52)
Severe impairment	62% (47/76)	36% (19/52)

<sup>a</sup>One patient who was not tested at 3 mos was assessed at 12 mos, and 14 patients who were tested at 3 mos were not assessed at 12 mos for reasons other than death.

To determine whether duration of delirium is an independent predictor of long-term cognitive impairment, we used multiple nonlinear regression to analyze the associations between days of delirium and summary scores of cognitive performance at 3-mo and 12-mo follow-up, adjusting for covariates. All covariates were included in the regression models, regardless of statistical significance. Nonlinearity of the association between duration of delirium and cognitive performance was assessed by inclusion of restricted cubic splines in the regression models. To correct for possible overfitting in the main analyses, we also conducted sensitivity analyses using a propensity score to reduce the number of covariates included in the models predicting cognitive

performance. Propensity score adjustment, commonly used to control for many potential confounders at once without compromising analytical power, is often used when analyzing the effect of a dichotomous exposure (e.g., a specific intervention) and has more recently been applied to the analysis of ordinal or continuous exposures (43). A propensity score for each patient was generated using a proportional odds logistic regression model whose dependent variable was days of delirium as a function of six covariates: age, education, preexisting cognitive function, severity of illness, sepsis, and treatment group. This propensity score was included with duration of delirium and sedative doses in the multiple nonlinear regression models, with summary scores of cognitive performance at 3-mo and 12-mo follow-up as the outcomes.

Because duration of delirium correlates with duration of critical illness, especially with duration of mechanical ventilation, we considered the possibility that delirium duration is not a specific predictor of poor long-term cognitive outcomes but rather is a surrogate for duration of mechanical ventilation. Thus, to determine whether duration of mechanical ventilation is a predictor of long-term cognitive impairment, we removed delirium days from the multiple nonlinear regression models previously described and replaced this variable with ventilator days. We used R (version 2.8.1 patched) for all statistical analyses (44).

## RESULTS

From October 2003 to March 2006, 187 patients were enrolled in the clinical trial (23) at Saint Thomas Hospital (Fig. 1); 54 of these patients died in the hospital, and seven met other criteria for exclusion from this prospective cohort study (three had large strokes before discharge, one underwent cardiac bypass surgery, one underwent neurosurgery, and two had been enrolled in the trial despite advanced Alzheimer's dementia). The remaining 126 patients were eligible for the current cohort study. Before being tested at 3-mo follow-up, however, 27 of these patients died, 11 withdrew, and nine were lost to follow-up. Follow-up was completed in July 2007; of the 99 patients who survived  $\geq 3$  mos after enrollment, cognitive outcomes were obtained for 77 (78%) patients at 3-mo and/or 12-mo follow-up. The 22 patients who survived  $\geq 3$  mos after enrollment but were never tested had demographics and clinical characteristics similar to the 77 patients who were tested.

The cohort, half of whom were 61 yrs of age or older, had a high severity of illness on ICU admission (Table 1). Only 9% of patients in the cohort had evidence of preexisting cognitive impairment according to the Short Informant Questionnaire of Cognitive Decline in the Elderly; alternatively, delirium was common during the ICU stay. Eighty-four percent of patients had delirium in the ICU, with half the patients delirious for  $\geq 2$  days and one in four patients delirious for  $\geq 5$  days. The median duration of delirium among the 22 patients who withdrew or were lost to follow-up was 2 (interquartile range, 1–3) days compared with 2 (interquartile range, 1–5) days among the 77 patients who were followed-up ( $p = .61$ ).

Cognitive impairment was common throughout follow-up; nearly 80% of patients tested 3 mos after their ICU stay were cognitively impaired (Table 2). Although the number of patients with severe cognitive impairment decreased some from 3-mo to 12-mo follow-up,  $>70\%$  of patients tested remained impaired 1 yr after their critical illness and more than one in three was severely impaired 1 yr after their ICU stay (Table 2). Among the 29 patients with severe cognitive impairment at 3 mos who were tested at 12 mos, 16 remained severely impaired at 12 mos, 11 had mild to moderate impairment and only two no longer had impairment.

Table 3. Associations of intensive care unit exposures with long-term cognitive outcomes

Predictor	Multivariable Regression Results		
	Point Estimate <sup>a</sup>	95% Confidence Interval	P
Delirium days (interquartile range, 1–5)			
Association with 3-mo outcome	−4.6	−9.2 to −0.1	.02
Association with 12-mo outcome	−6.9	−12.7 to −1.1	.03
Ventilator days (interquartile range, 2–10)			
Association with 3-mo outcome	3.0	−3.1 to 9.1	.20
Association with 12-mo outcome	−2.0	−10.1 to 6.2	.58

<sup>a</sup>The point estimate ( $\beta$  coefficient) indicates the change in mean T-score on the cognitive battery (representing average age-adjusted and education-adjusted performance across all nine neuropsychological tests) that is independently associated with an increase in the exposure—i.e., delirium days or ventilator days—from the 25<sup>th</sup> percentile value to the 75<sup>th</sup> percentile value. For example, an increase from 1 day of delirium (25<sup>th</sup> percentile) to 5 days (75<sup>th</sup> percentile) was independently associated with a nearly 5-point decline (i.e., one-half standard deviation worse) in the cognitive battery mean score at 3-mo follow-up. See further explanation in the text.

Duration of delirium in the ICU was an independent predictor of cognitive impairment 3 mos after enrollment (Table 3). As shown in Figure 2A, longer durations of delirium were associated with worse average performance on the comprehensive battery of neuropsychological tests administered at 3-mo follow-up after adjusting for age, education, preexisting cognitive function, severity of illness, severe sepsis, treatment group, and total exposure to sedatives in the ICU ( $p = .02$ ). An increase from 1 day of delirium to 5 days, for example, was independently associated with nearly a 5-point decline (i.e., a one-half sd decline) in the cognitive battery mean score (95% confidence interval, −9.2 to −0.1). Thus, whereas a “typical” patient in our cohort (i.e., one in whom all covariates were at their median or mode) who was delirious for 1 day in the ICU would be able to function cognitively on the lower boundary of “normal” 3 mos after their critical illness (performing all instrumental activities of daily living), a “typical” patient who was delirious for 5 days in the ICU would characteristically demonstrate deficits 3 mos later when performing complex tasks (such as those required to manage money, follow detailed instructions, read maps, and the like).

The association between delirium and long-term cognitive impairment persisted throughout follow-up such that longer durations of delirium in the ICU were still independently associated with worse cognitive performance a full year after enrollment (Table 3 and Fig. 2B). An increase from 1 day of delirium to 5 days, in fact, was associated with decline of almost 7 points in the cognitive battery mean score at 12-mo follow-up ( $p = .03$ ).

Unlike duration of delirium, duration of mechanical ventilation did not predict cognitive impairment at either 3-mo or 12-mo follow-up (Table 3), indicating that delirium is a specific predictor of poor long-term cognitive outcomes and is not simply a surrogate for duration of mechanical ventilation. Additionally, sensitivity analyses using propensity scores to summarize the effect of multiple covariates yielded similar results regarding delirium duration’s association with long-term cognitive outcomes (data not shown), indicating that the results of these multivariable analyses were not significantly biased by overfitting.

## DISCUSSION

This prospective cohort study is the first investigation to our knowledge to identify delirium as an independent predictor of long-term cognitive impairment among medical ICU patients attempting to recover from critical illness requiring mechanical ventilation. Whereas it is known that the occurrence and duration of delirium in the ICU predict increased mortality (15, 22, 45), this investigation found that duration of ICU delirium (in contrast with duration of mechanical ventilation) is an independent predictor of long-term cognitive impairment up to 1 yr after critical illness in this patient population. These data are important to the health care of critically ill patients, a large and growing population of patients who are greatly concerned with recovery of cognitive function after severe illness (46). Future interventional trials should focus on mechanically ventilated ICU patients with delirium, especially those delirious for several days or more, in their

attempts to understand and improve the cognitive outcomes of critically ill patients.

Whereas dozens of publications during the past 25 yrs have reported on cognitive impairment experienced by cardiac surgery patients (39, 47), this complication was discovered relatively recently in the rapidly growing population of non-cardiac surgery patients with critical illness. Although gradual recovery is noted in some patients (10), the incidence of long-term cognitive impairment among general medical and surgical ICU survivors is consistently high across studies (2), and the emerging clinical picture is often one of a dementia-like illness. In a landmark investigation, Hopkins et al (8) assessed 55 patients 1 yr after mechanical ventilation for acute respiratory distress syndrome and found that 78% were impaired in one or more neurocognitive domains, including memory, attention, concentration, and mental processing speed. Subsequently, other investigators have confirmed that ICU survivors are at high risk for cognitive impairment that may persist years after recovery from critical illness (3, 9–14). Rothenhausler et al (3), for example, examined cognitive outcomes, employment status, and health-related quality of life among 46 acute respiratory distress syndrome survivors years after discharge and found that 11 (24%) had cognitive impairment, which was associated with an inability to return to work and poor health-related quality of life. Despite using conservative definitions, we found somewhat higher rates of cognitive impairment than those previously reported; 72% of ICU survivors had cognitive impairment at 1-yr follow-up (and more than one in three had severe impairment), possibly because our cohort was much older than those previously studied.

Several studies among older inpatients without critical illness (i.e., non-ICU patients) have found that delirium is associated with long-term cognitive impairment (19–21, 48–52), but no previous studies have examined delirium duration and long-term cognitive outcomes in ICU survivors. Based on their findings, Francis and Kapoor (48) proposed that delirium is a marker of impaired brain reserve attributable to chronic disease or subclinical dementia; indeed, it is possible that a significant proportion of the patients studied in non-ICU cohorts, which included only older participants, had undiagnosed dementia or mild cog-

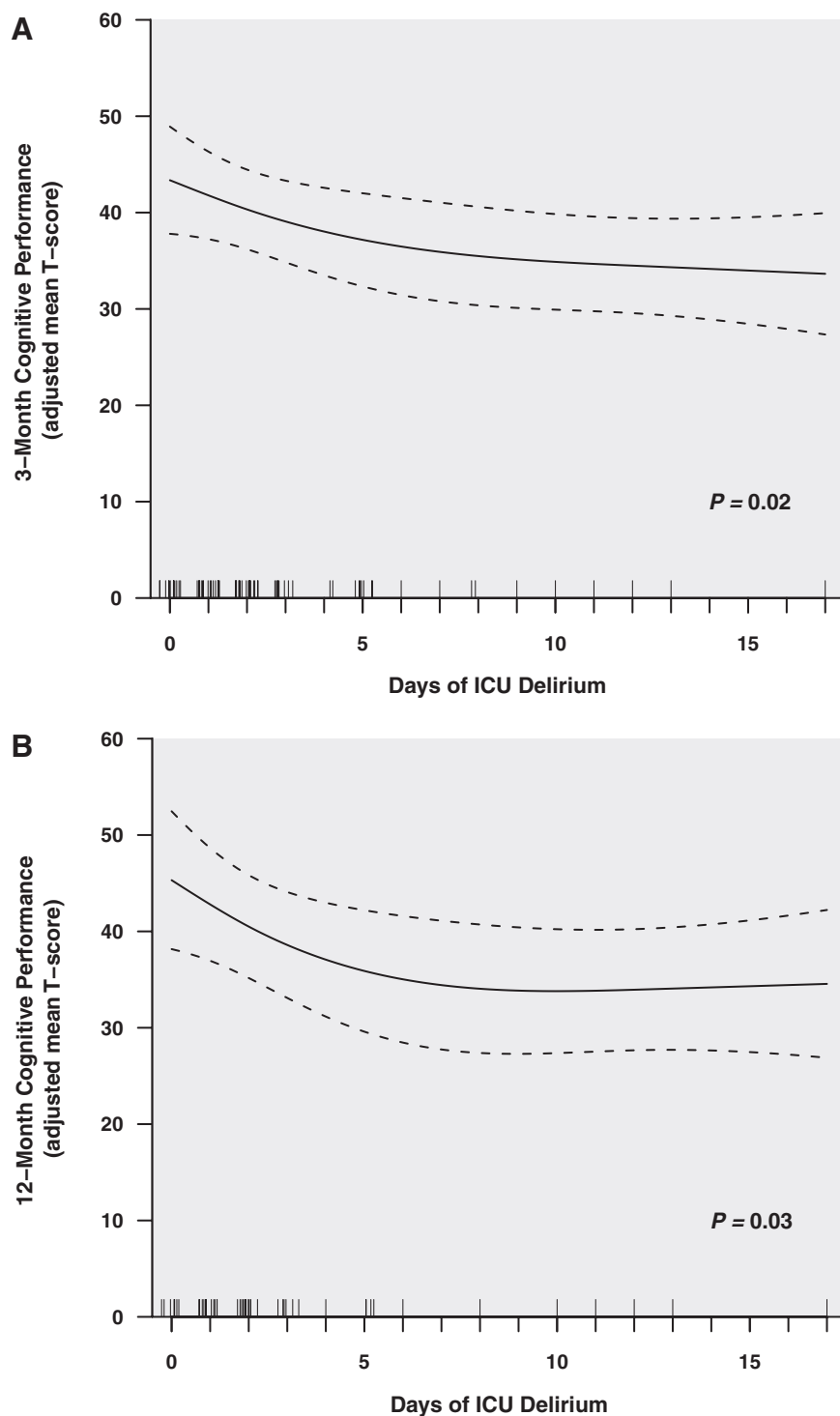


Figure 2. Relationship between duration of delirium and average cognitive performance measured at 3-mo and 12-mo follow-up. At 3-mo (A) and 12-mo follow-up (B), duration of delirium independently predicted average performance on a battery of nine neuropsychological tests after adjusting for age, education, preexisting cognitive function, severity of illness, severe sepsis, Awakening and Breathing Controlled Trial treatment group, and total benzodiazepine, opiate, and propofol doses administered in the intensive care unit ( $p = .02$  and  $0.03$ , respectively). A mean T-score (shown on the y-axis) of 50 indicates average performance on nine neuropsychological tests, based on age-adjusted and education-adjusted normative data. These results show that, other factors being equal, a patient with 5 days of delirium will score, on average, nearly one-half of a standard deviation lower (i.e., 5 points lower) across domains of cognitive function at 3-mo follow-up (and 7 points lower at 12-mo follow-up) than a patient who was delirious for 1 day. The smooth graphs were created using restricted cubic splines. A rug plot indicates the distribution of delirium duration in the cohort; specifically, each patient is represented by a vertical bar sitting on the x-axis, showing the duration of that patient's delirium (jittering is used to display all patients, although only integers were used to record delirium days). ICU, intensive care unit.

nitive impairment, a syndrome thought to be a precursor to dementia (53). Thus, the dementia diagnosed during follow-up in these populations may represent progression of a preexisting disease. The severity of long-term cognitive impairment, however, observed in survivors of critical illness, many of whom are young patients unlikely to have preexisting disease, suggests that the persistent cognitive impairment observed in these patients is acquired by many during their critical illness. Even among those critically ill patients with preexisting cognitive impairment, delirium may be a predictor of acceleration of cognitive decline, as was recently demonstrated in a cohort of non-ICU hospitalized patients with Alzheimer's disease (20). Future research, ideally assessing patients before and after critical illness, is needed to determine whether delirium is an indicator of new-onset cognitive impairment or if it occurs primarily as a result of preexisting cognitive impairment. In either case, delirium in the ICU has great prognostic value when routinely monitored using validated tools (25, 54), a practice not yet widely adopted (55) despite evidence that delirium typically goes unrecognized when such tools are not used (56). Delirium may be an excellent short-term measure of the effectiveness of central nervous system-focused therapies in the ICU. Future interventional trials should determine whether reductions in delirium duration in response to therapies directed at mitigating acute brain dysfunction can predict improved long-term outcomes, including survival and long-term cognitive impairment.

Although delirium in the ICU is diagnosed (25, 26, 54) using the same criteria as delirium outside of the ICU (57), several important features of ICU delirium mandate distinct approaches to investigation. First, delirium affects up to 80% of certain critically ill populations, e.g., mechanically ventilated ICU patients (15, 18), compared with <15% of non-ICU hospitalized patients (58). Also, non-ICU patients are considered at high risk for delirium when they have >3 risk factors (59, 60), whereas patients in the ICU are exposed on average to 10 or more risk factors for delirium (61). Two potent risk factors for delirium that are disproportionately common in the ICU as compared with non-ICU settings are severe sepsis and exposure to very large quantities of sedative medications. These notable differences between ICU delirium and delirium on the hospital ward, as well as



the very high incidence of persistent cognitive impairment after critical illness, have driven others to call for investigations such as this cohort study (62).

Our study has several limitations that warrant comment. The single-center design and nesting within a clinical trial reduces sample size and limits generalizability to populations similar to those we enrolled. Although we were able to assess patients for delirium on 893 (96.2%) of 928 patient-days, this exposure variable was missing on 3.8% of patient-days; missing assessments were considered nondelirious. Because depression and posttraumatic stress disorder can contribute to cognitive impairment (63, 64), these disorders may confound the relationship between delirium and long-term cognitive impairment. In this study, we did not adjust for posttraumatic stress disorder or depression, which affect 15% to 50% of ICU survivors, because of limited sample size and because previous studies have found no association between ICU delirium and these psychological outcomes (65). Future studies should examine the effects of psychological dysfunction on cognitive impairment among ICU survivors. With 10 independent variables and a nonlinear term included in our analyses, the regression models may have been susceptible to overfitting, but sensitivity analyses using a data reduction technique confirmed our findings. Last, as in any study of nonelective ICU patients, we were unable to directly measure premorbid cognitive function and therefore followed the example of previous studies that evaluated patients with acute, unanticipated illnesses or injury (66) using a surrogate instrument to assess premorbid cognitive function. The instrument we used, the Short Informant Questionnaire of Cognitive Decline in the Elderly (30, 31), has been shown in numerous studies to be highly reliable (Cronbach's alpha, 0.93–0.97), sensitive (75%–100%), and specific (68%–86%) as a screening test for dementia (67). It is possible, nevertheless, that subclinical or mild cognitive impairment was not identified using the Informant Questionnaire on Cognitive Decline in the Elderly.

## CONCLUSIONS

In conclusion, this investigation found that duration of delirium in mechanically ventilated medical ICU patients is a predictor of cognitive impairment up to 1 yr after critical illness. In light of the recently recognized public health problem of ICU-

acquired long-term cognitive impairment manifesting as a dementia-like illness (68), the identification of a clinical predictor for this complication could have large implications for prognostication and the design of future clinical trials aimed at reducing the burden of brain dysfunction among critically ill patients. There are many candidate approaches to reducing the overall "dose" of acute brain dysfunction, from protocolization of care (58, 69) to specific pharmacologic strategies (23, 70–74), that might, in time, prove helpful for the preservation of cognitive function among the millions of ICU patients treated every year.

Participants in this CME activity will be able to better predict the presence of long-term cognitive impairment in mechanically ventilated ICU patients.

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