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Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit.

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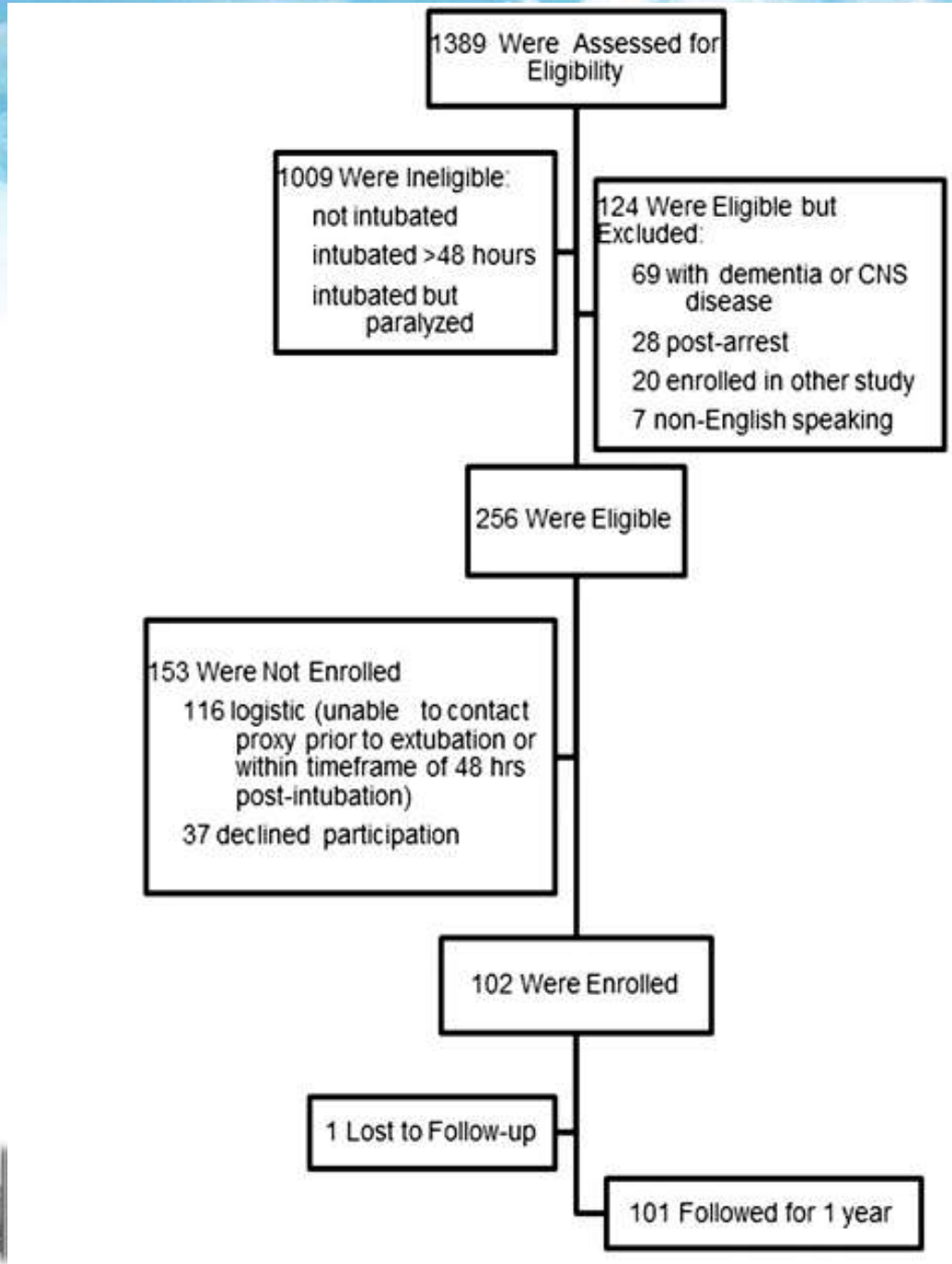
- **Rationale:** Intensive care unit (ICU) delirium is associated with ventilator, ICU, and hospital days; discharge functional status; and mortality. Whether rapidly reversible, sedation-related delirium (delirium that abates shortly after sedative interruption) occurs with the same frequency and portends the same prognosis as persistent delirium (delirium that persists despite a short period of sedative interruption) is unknown.
- **Methods:** This was a prospective cohort study of 102 adult, intubated medical ICU subjects in a tertiary care teaching hospital. Confusion Assessment Method for the ICU evaluation was performed before and after daily interruption of continuous sedation (DIS). Investigators were blinded to each other's assessments and as to whether evaluations were before or after DIS. The primary outcome was proportion of days with no delirium versus rapidly reversible, sedation-related delirium versus persistent delirium. Secondary outcomes were ventilator, ICU, and hospital days; discharge disposition; and 1-year mortality.

- **Measurements and Main Results:** The median proportion of ICU days with delirium was 0.57 before versus 0.50 after DIS ($P < 0.001$). The Confusion Assessment Method for the ICU indicated patients are 10.5 times more likely to have delirium before DIS versus after ($P < 0.001$). Rapidly reversible, sedation-related delirium showed fewer ventilator ($P < 0.001$), ICU ($P = 0.001$), and hospital days ($P < 0.001$) than persistent delirium. Subjects with no delirium and rapidly reversible, sedation-related delirium were more likely to be discharged home ($P < 0.001$). Patients with persistent delirium had increased 1-year mortality versus those with no delirium and rapidly reversible, sedation-related delirium ($P < 0.001$).
- **Conclusions:** Rapidly reversible, sedation-related delirium does not signify the same poor prognosis as persistent delirium. Degree of sedation should be considered in delirium assessments. Coordinating delirium assessments with daily sedative interruption will improve such assessments' ability to prognosticate ICU delirium outcomes.

- The numerous potential contributors to ICU delirium, including sepsis, hypoxemia, structural brain injury, sleep deprivation, and medication effects, likely operate via different mechanisms with different degrees of reversibility.
- To date, the published outcomes research on ICU delirium has grouped patients with this syndrome into a single diagnostic category without reference to its very heterogeneous antecedents, this may be an oversimplification.
- Although sedatives and analgesics are risk factors , the extent to which ICU delirium can be attributed to these commonly used medications is not well understood.
- Furthermore, it is unknown whether rapidly reversible, sedation-related delirium (delirium that abates quickly after sedative interruption) differs from persistent delirium (delirium that persists despite a short sedative interruption period) with respect to the ominous outcomes previously reported.

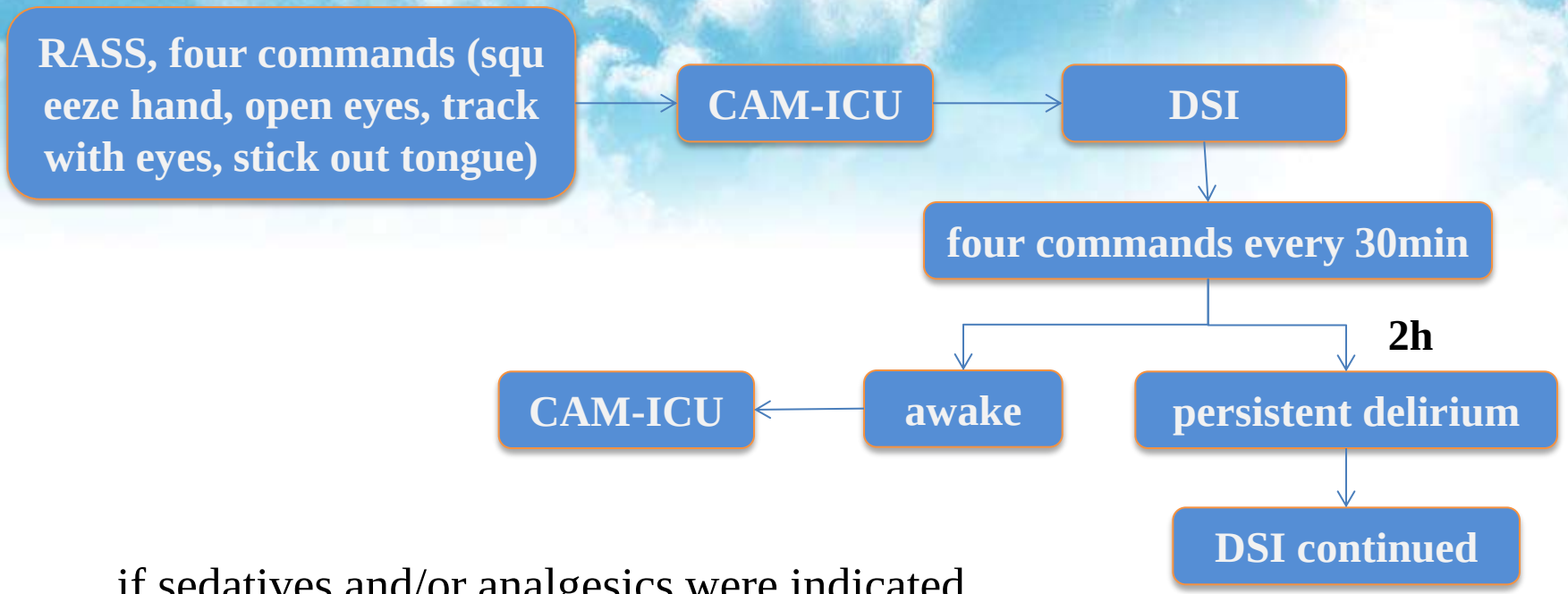
method

- From July 2009 through June 2010 and October 2010 through April 2011 we screened 1,389 consecutive medical ICU admissions.
- Patients 18 years or older intubated less than 48 hours on a protocol of daily interruption of continuous sedatives and analgesics were eligible for inclusion .
- According to this protocol, patients underwent daily sedative interruption unless they were receiving a sedative infusion for active seizures or alcohol withdrawal, were receiving escalating sedative doses due to ongoing agitation, were receiving neuromuscular blockers, had evidence of active myocardial ischemia in the previous 24 hours, or had evidence of increased intracranial pressure . The sedation protocol targeted a Richmond Agitation-Sedation Scale (RASS) of 0 to −2, with bedside nurse recording every 4 hours.
- Patients with dementia, central nervous system disease, cardiac arrest, enrollment in another study, or non-English speaking status were excluded.


1389 Were Assessed for Eligibility
1009 Were Ineligible:
not intubated
intubated >48 hours
intubated but paralyzed
124 Were Eligible but Excluded:
69 with dementia or CNS disease
28 post-arrest
20 enrolled in other study
7 non-English speaking
256 Were Eligible
153 Were Not Enrolled
116 logistic (unable to contact proxy prior to extubation or within timeframe of 48 hrs post-intubation)
37 declined participation
102 Were Enrolled
1 Lost to Follow-up
101 Followed for 1 year

Study Protocol

- Each day two different investigators assessed the subjects—one before and one after daily sedative interruption. The two investigators performing bedside assessments were blinded to sedative/analgesic infusion(s); they were also blinded to each other's assessments.
- Investigators were not involved in patient care and had no contact with daily ICU activities.
- All subjects underwent a daily spontaneous breathing trial after sedative interruption (unless sedative interruption could not be performed for reasons listed above).



if sedatives and/or analgesics were indicated for agitation or hypoxia before 2 hours, they were assessed immediately before restarting the sedatives and/or analgesics

Once sedation and analgesia were discontinued permanently, subjects were assessed with the CAM-ICU once daily until ICU discharge

Outcome Measures

- The primary outcome was the proportion of days of: no delirium (definition: subjects with negative CAM-ICU assessment both before and after sedative interruption) versus rapidly reversible, sedation-related delirium (definition: delirium by CAM-ICU assessment that abated within 2 hours of sedative interruption) versus persistent delirium (definition: delirium by CAM-ICU assessment that persisted beyond 2 hours of sedative interruption) versus mixed delirium (definition: delirium assessments that varied from day to day between rapidly reversible, sedation-related, and persistent).
- Secondary outcome measures included association of CAM-ICU assessments before and after daily interruption of sedation with: ventilator, ICU, and hospital days; hospital discharge disposition ([1] home, [2] ongoing institutional care, [3] hospice/death); and 1-year mortality.
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Statistical Analysis

- To achieve 80% power to detect a decrease of delirium from 80 to 60% (two-sided $\alpha = 0.05$) in post–sedative interruption assessment, approximately 100 patients were needed.
- We used Kruskal-Wallis tests or analysis of variance to compare continuous variables and $\chi 2$ tests or Fisher exact tests to compare categorical variables between different groups. Paired continuous and categorical data were analyzed using Wilcoxon signed-rank tests and McNemar testsrespectively. The effect of sedative interruption on the presence of delirium was analyzed by mixed-effects logistic regression with a random patient effect. To compare the effect of delirium category on 1-year mortality, we used survival analysis. Comparison of survival between groups was performed using the log-rank test. The cumulative number of ICU days of delirium was a time-varying covariate in Cox regression models. The proportional hazards assumption was verified using Schoenfeld residuals. Cox regression was also used for the analysis of hospital and ICU lengths of stay and length of mechanical ventilation.

Results

Table 1: Baseline Characteristics of the Study Patients

	Overall	ND	RRD	PD	Mixed
N	102	10	12	51	24
Age, yr	59.8 (49.1, 70.0)	46.7 (42.8, 57.6)	46.2 (37.1, 68.8)	60.6 (51.9, 70.1)	63.7 (53.5, 82.0)
Men	57 (55.9)	6 (60.0)	7 (58.3)	27 (52.9)	12 (50.0)
APACHE II score	21.5 (17, 28)	13.5 (9, 17)	21 (14, 25)	22 (18, 29)	23 (18.5, 29)
ICU admission diagnosis					
Acute hypoxic respiratory failure	35 (34.3)	2 (20.0)	3 (25.0)	17 (33.3)	9 (37.5)
Ventilatory failure	22 (21.6)	2 (20.0)	4 (33.3)	13 (25.5)	3 (12.5)
Sepsis	22 (21.6)	1 (10.0)	1 (8.3)	14 (27.5)	5 (20.8)
Gastrointestinal hemorrhage	9 (8.8)	0 (0)	2 (16.7)	4 (7.8)	3 (12.5)
Airway compromise	7 (6.9)	3 (30.0)	1 (8.3)	1 (2.0)	2 (8.3)
Other	7 (6.9)	2 (20.0)	1 (8.3)	2 (3.9)	2 (8.3)

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; ICU = intensive care unit; Mixed = mixed delirium; ND = no delirium; PD = persistent delirium; RRD = rapidly reversible, sedation-related delirium.
Data are presented as median (IQR) or N (%). APACHE II scores can range from 0 to 71, with higher scores indicating more severe illness. *P* value for age = 0.10 (Kruskal-Wallis test). *P* value for APACHE II < 0.001 (Kruskal-Wallis test). ND is significantly different from the RRD, PD, and mixed groups, but the RRD, PD, and mixed groups are not significantly different from one another. *P* value for sex = 0.35 (Fisher exact test). *P* value for admission diagnosis = 0.23 (Fisher exact test).

Table 3: Comparison of Propofol, Midazolam, and Fentanyl Use per Ventilator Day between Groups

	ND	RRD	PD	Mixed	*P* Value
N	10	12	51	24	
Propofol, mg	2,717.3 (720.9, 4,921.1)	2,420.4 (646.9, 2,714.7)	1,262.6 (644.7, 2,756.8)	990.9 (468.9, 2,368.2)	0.46
Midazolam, mg	0 (0, 16.3)	0.4 (0, 3.9)	0.7 (0, 8.7)	0 (0, 0.5)	0.32
Fentanyl, μg	1,730 (755.8, 2,599.3)	1,843.1 (773.2, 2,408.9)	907.9 (412.1, 1,976.1)	700.9 (411.9, 1,364.2)	0.25

Definition of abbreviations: Mixed = mixed delirium; ND = no delirium; PD = persistent delirium; RRD = rapidly reversible, sedation-related delirium.

Results

- Subjects were 10.5 times (95% confidence interval, 5.3–21.0; P < 0.001) more likely to be classified as delirium when assessed before sedation interruption compared with after sedation interruption.
- The median (IQR) proportion of ICU days with delirium was 0.57 (0.33, 0.89) pre–sedation interruption versus 0.5 (0.13, 0.84) post–sedation interruption; (*P* < 0.001). The median number of delirium days measured pre–sedation interruption was 4 (1, 7), versus 3 (1, 6) post–sedation interruption; (*P* < 0.001).
- Regarding prevalence of delirium, 89% of subjects had at least 1 day of delirium when assessed before sedation interruption versus only 77% when assessed after sedation interruption (*P* = 0.003).

Results

Table 4: Outcomes for Mechanical Ventilation Days and Length of Stay

	ND	RRD	Mixed	PD	Overall *P* Value
Days of MV	2.4 (1.3, 3.1)	2.5 (1.6, 2.8)	5.1 (2.2, 12.0)	6.2 (3.7, 12.0)	
ICU LOS	4.0 (2.4, 8.1)	4.5 (2.2, 7.2)	9.7 (6.0, 17.7)	13.1 (8.8, 19.1)	
Hospital LOS	8.1 (7.7, 16.9)	6.7 (3.8, 16.4)	26.8 (9.8, 50.0)	25.4 (13.6, 29.6)	
HR for fewer days of MV	3·83 (1.82, 8.06) $P < 0.001$	4.10 (2.00, 8.38) $P < 0.001$	0.65 (0.36,1.17) $P = 0.15$	Reference	<0.001
Adjusted HR for fewer days of MV*	3.38 (1.43, 8.02) $P = 0.006$	3.92 (1.88, 8.16) $P < 0.001$	0.64 (0.35,1.15) $P = 0.14$	Reference	<0.001
HR for shorter ICU LOS	2.49 (1.18, 5.24) $P = 0·02$	3.15 (1.59, 6.22) $P = 0.001$	0.78 (0.45, 1.34) $P = 0.37$	Reference	0.001
Adjusted HR for shorter ICU LOS*	2.27 (0.92, 5.58) $P = 0·08$	3.07 (1.53, 6.15) $P = 0.002$	0.77 (0.45, 1.33) $P = 0.35$	Reference	0.002
HR for shorter hospital LOS	3.96 (1.79, 8.76) $P = 0.001$	3.47 (1.74, 6.95) $P < 0·001$	1.18 (0.64, 2.17) $P = 0.60$	Reference	<0.001
Adjusted HR for shorter hospital LOS*	1.59 (0.63, 3.98) $P = 0.32$	3.05 (1.52, 6.13) $P = 0.002$	0.97 (0.52, 1.80) $P = 0.92$	Reference	0.008

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; HR = hazard ratio; ICU = intensive care unit; LOS = length of stay; Mixed = mixed delirium; MV = mechanical ventilation; ND = no delirium; PD = persistent delirium; RRD = rapidly reversible, sedation-related delirium. *HRs are adjusted for APACHE II score.

- ND had fewer ventilator ($P < 0.001$), ICU ($P = 0.02$), and hospital days ($P = 0.001$) than the PD.
- RRD also had fewer ventilator days ($P < 0.001$), ICU days ($P = 0.001$), and hospital days ($P < 0.001$) than PD.
- There were no significant differences between ND and RRD.

Results

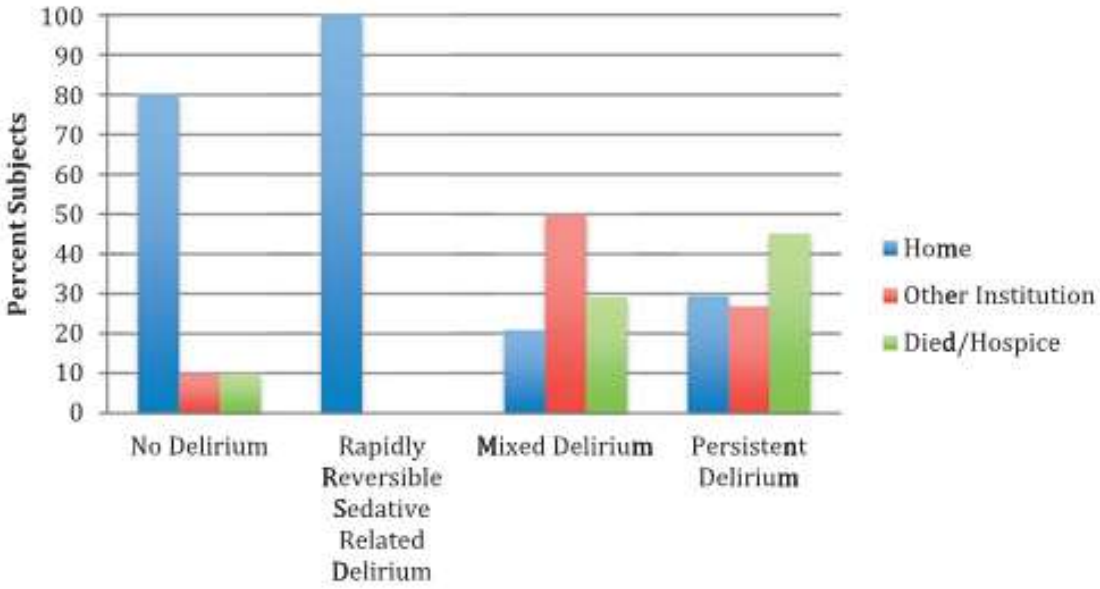
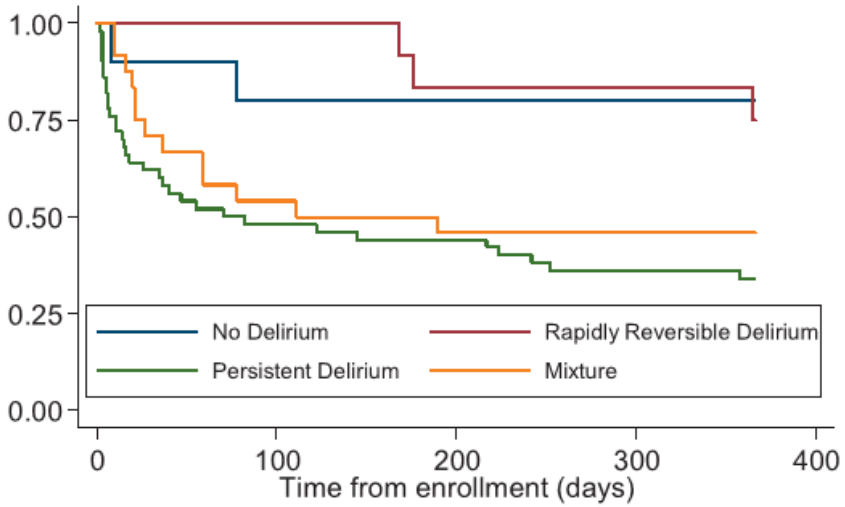


Figure 2. Discharge location of subjects by Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) results.

Results

A



Number at risk					
No Delirium	10	8	7	7	0
Rapidly Reversible Delirium	12	12	10	10	0
Persistent Delirium	51	24	22	18	0
Mixture	24	13	11	11	0

B

	HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
Additional Number of Days of Rapidly Reversible, Sedation-Related Delirium	0.90 (0.67, 1.21)	0.48	0.90 (0.67, 1.21)	0.49
Additional Number of Days of Persistent Delirium	1.14 (1.09, 1.20)	<0.001	1.13 (1.08, 1.18)	<0.001

Figure 3. (*A*) One-year mortality by Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) results. (*B*) Hazard ratio (HR) of delirium for death. APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval.

- Each additional day of persistent delirium was associated with a 14% increased risk of death by 1 year ($P < 0.001$). In contrast, days of rapidly reversible, sedation-related delirium were not associated with any increased risk of death by 1 year

Discussion

- This study provides direct evidence that the timing of sedative drug administration must be accounted for to provide the most accurate assessment of ICU delirium.
- It may be useful in future studies to assess whether delirium screening with CAM-ICU should be done only with RASS scores of 0 or greater.
- Our study clearly shows that sedative-induced delirium is very different and clearly less dangerous. patients with ICU delirium that abated rapidly after sedative interruption did not differ from patients with no delirium.
- Whether awakening patients from sedation every day in our current trial improved their outcomes directly or merely identified an important group who were misclassified as delirium cannot be determined from our study.

limitations

- First, although we attempted to keep variables except sedative and analgesic medications constant, it is possible that other risk factors for delirium were changing and uncontrollable.
- Second, it is possible that 2 hours of sedative interruption may not have been a sufficient washout period.
- Third, this was a single-center study with a relatively small number of patients; however, the extremely high levels of statistical significance for the outcomes suggest that larger numbers would not likely lead to different results.
- Fourth, the patients in the persistent delirium group clearly had higher illness acuity than the other groups, as demonstrated by imbalances in their demographic data.
- Last, a small proportion of study days (16%) did not have delirium assessments both before and after DIS because of inability to interrupt sedation.

Thank You !

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