HHS Public Access

Author manuscript

Crit Care Med. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Crit Care Med. 2017 April ; 45(4): 584–590. doi:10.1097/CCM.0000000000002250.

Pediatric Delirium in Critically-Ill Children: An International Point Prevalence Study

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DISCLOSURES: All authors confirm that they have no conflicts of interest to declare in relation to this manuscript.
Copyright form disclosure: The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Abstract

Objective—To determine prevalence of delirium in critically-ill children and explore associated risk factors.

Design—Multi-institutional point-prevalence study.

Setting—Twenty-five pediatric critical care units in the United States, the Netherlands, New Zealand, Australia, and Saudi Arabia.

Patients—All children admitted to the pediatric critical care units on designated study days (n=994).

Intervention—Children were screened for delirium using the Cornell Assessment of Pediatric Delirium (CAPD) by the bedside nurse. Demographic and treatment-related variables were collected.

Measurements and Main Results—Primary study outcome measure was prevalence of delirium. In 159 children, a final determination of mental status could not be ascertained. Of the 835 remaining subjects, 25% screened positive for delirium, 13% were classified as comatose, and 62% were delirium-free and coma-free. Delirium prevalence rates varied significantly with reason for ICU admission, with highest delirium rates found in children admitted with an infectious or inflammatory disorder. For children who were in the PICU for 6 or more days, delirium prevalence rate was 38%. In a multivariate model, risk factors independently associated with development of delirium included age < 2 years, mechanical ventilation, benzodiazepines, narcotics, use of physical restraints, and exposure to vasopressors and anti-epileptics.

Conclusions—Delirium is a prevalent complication of critical illness in children, with identifiable risk factors. Further multi-institutional, longitudinal studies are required to investigate effect of delirium on long-term outcomes, and possible preventive and treatment measures. Universal delirium screening is practical and can be implemented in pediatric critical care units.

Keywords

delirium; pediatric; prevalence; critical care; neurocritical care; point prevalence

INTRODUCTION

Delirium is acute neurologic dysfunction in the setting of serious illness. It is characterized by a fluctuating disturbance in cognition and awareness, and is a result of an underlying medical condition, and/or its treatment. Delirium is generally a temporary state, reversing as the underlying condition abates or when iatrogenic triggers are removed(1). Delirium in adults with critical illnesses is well characterized since it is associated with increased mortality, and significant morbidity(2–4). It is linked to in-hospital death, and long-term cognitive impairment in survivors(5–7). Delirium increases time to extubation, hospital length of stay (LOS), and medical costs(8–10).

Much less is known about pediatric delirium (PD), largely due to lack of widespread screening(11–13). Recent years have seen the advent of three validated screening tools for use in the pediatric intensive care unit (PICU): the Pediatric Confusion Assessment Method

for the ICU (pCAM-ICU), the Preschool Confusion Assessment Method for the ICU (psCAM-ICU), and the Cornell Assessment of Pediatric Delirium (CAPD). The pCAM-ICU is an interactive, cognitively-oriented tool designed for children over age 5(14). Similarly, the psCAM-ICU is an interactive tool used in children 6 months to 5 years of age(15). Neither is validated for use in children with developmental delay. The CAPD is a strictly observational tool, designed for children of all ages and developmental abilities(16). All were developed for use by the bedside provider, allowing for rapid, real-time delirium screening in PICUs. A recent position statement by the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) recommended use of CAPD as an instrument to assess paediatric delirium in critically ill infants and children (grade of recommendation =A) (17).

An emerging body of pediatric research indicates that delirium is a common complication of childhood illness, with a prevalence greater than 20 percent(12,16). PD has been associated with severity of illness, age less than 5 years, sedation, and mechanical ventilation (MV) (18–20). PD has been linked to significant increase in hospital length of stay, and post-traumatic stress symptoms and delusional memories in child survivors(18,21,22). However, most PD research has been limited by retrospective design, narrow inclusion criteria, small number of subjects, and single-center studies(11). To date, there has been no large-scale multi-institutional approach to defining the scope of PD. We hypothesized that delirium prevalence would be >20% overall, and would be more frequent in patients who had been in the ICU for a longer period of time (>3 days) (12,16). We hypothesized that risk factors associated with development of delirium would include mechanical ventilation, sedation (specifically narcotics and benzodiazepines), use of restraints, and younger age (less than 5 years old) (18–20).

Our objectives were to determine the prevalence of PD in critically-ill children in diverse institutions, on 2 separate study dates, and determine demographic and treatment-related risk factors for the development of PD. A secondary objective was to establish the practicality of multi-institutional bedside screening for delirium.

MATERIALS AND METHODS

Study Design and Subject Accrual

Each site received ethics approval from its local Institutional Review Board (IRB) and was granted waiver of informed consent for this observational, minimal risk study. Weill Cornell Medical College (WCMC) served as the data coordinating center (DCC). For the purpose of this study, the CAPD was chosen as the delirium screening tool (supplemental data file 1) because it is the only tool that has been validated across the entire pediatric age range and for application in children with developmental delay, and it can successfully discriminate between delirium and other causes of altered mental status in PICU patients(16). It consists of eight items, scored on a Likert scale, with a cutoff of at least nine(16). Site selection was made by inviting members of the Pediatric Neurocritical Care Research Group (PNCRG) to participate in the study. Participating site principal investigators and research coordinators each viewed a short on-line educational video and then were certified by completing a test on the relevant study procedures including use of the CAPD tool.

On designated study days, every child physically admitted to the pediatric critical care unit at 8 am local time was included in analysis. Medical records were examined for demographics (age, sex, race, ethnicity), reason for admission, presence of physical restraints, respiratory support, and exposure to specific medications on the study day. Site personnel approached each child's bedside nurse in the afternoon, after a minimum of 4 hours into the nurse's shift, and completed the CAPD based on the nurse's clinical observations over the previous hours. To assist with providing a developmental framework for the youngest (i.e., pre-verbal) children, a developmental anchor point chart was available for use as a point-of-care reference when needed(23). Clinical care, including the depth of sedation, was not altered in conducting this study.

CAPD Scoring and Data Analysis

Consistent with other delirium research, children who were deeply sedated or pharmacologically paralyzed (no response to verbal stimulation) were categorized as "comatose" for this analysis(2, 9, 16); this is consistent with a Richmond Agitation Sedation Scale (RASS) score of -4 or -5. For all other developmentally typical children, a CAPD score ≥ 9 was considered a positive delirium screen and categorized as "delirious". Developmentally delayed children were categorized as "delirious" if they had a CAPD score ≥ 9 and the bedside nurse confirmed alteration from the child's baseline mental status. If the nurse could not confirm alteration of consciousness, these children were categorized as "unknown delirium state".

Data was collected by the site and uploaded to the DCC using REDCap electronic data capture system hosted at WCMC. REDCap (Research Electronic Data Capture) is a secure, web-based application providing an intuitive interface for validated data entry. No protected health information was shared between sites.

Statistical analysis

Variables were summarized with counts and percentages, or median and interquartile range. The description of subjects is based on the entire cohort. Delirium prevalence is based on the subjects that were comatose, delirious, or delirium/coma-free (excluding patients with unknown delirium state). Univariate and multivariate analyses compared those subjects who were delirious with those who were delirium/coma-free. The Wilcoxon rank-sum test and Fisher's exact test were used to determine univariate associations with delirium. For tables larger than 2 by 2, a Monte Carlo approximation to Fisher's exact test was used. All tests used a two-sided alternative, and p-values less than 0.05 were considered significant. Multivariate logistic regression was used to assess multivariate associations with delirium. A stepwise selection process with entry criteria of $p = 0.05$ was used to select variables that were independently associated with delirium. Variables included in the final multivariate model are presented with odds ratios and the associated 95% confidence intervals.

RESULTS

Fifteen sites participated in the first study day – enrolling 416 children; 24 sites participated in the second study day – enrolling 578 children. In total, 25 different institutions and 994

subjects were included (supplemental data file 2). The majority of the sites (n = 21, 84%) were in the United States with additional sites in the Netherlands, New Zealand, Australia, and Saudi Arabia. Twenty-two PICUs were university-affiliated and three were in community hospitals. Number of PICU beds ranged from 10–81, with a median of 36 beds.

Preliminary analyses tested data from the two study days separately, but found no significant differences. Therefore, subsequent analyses represent combined data from the entire cohort. Subjects (n=994) are described in Table 1. A slight majority (n = 537, 54%) of children were male and the median length of PICU stay was 6 d [2 – 19 d]. A large proportion of children were admitted with a primary diagnosis involving respiratory disease (n = 415, 42%), followed by cardiac disease (n = 252, 25%) and neurologic disorders (n = 167, 17%). A significant portion of the children (n = 372, 38%) were identified as having developmental delay. Thirty-six percent (n = 355) were on MV and 43% (n = 427) received benzodiazepines on the study day.

Delirium status (delirium vs. comatose vs. delirium/coma-free) could be established in 84% of the children, as 159 children with developmental delay were excluded since the nurse could not confirm neurologic baseline to compare with current mental status in the limited time-frame available for the study. Other than presence of developmental delay, demographics of excluded subjects did not differ from the overall sample. Of the remaining 835 children, 25% were delirious, 13% were comatose, and 62% were delirium-free and coma-free (Figure 1). Delirium prevalence rates varied significantly among institutions, with a median of 23.3% (IQR 20.0 – 35.4%; p=0.038).

In univariate analyses (table 2), children with delirium were more likely to be < 2 years old, mechanically ventilated, exposed to vasopressors and anti-seizure medications, as compared to the rest of the cohort. Potentially modifiable risk factors included use of physical restraints, narcotics, sedatives, and steroids. Children diagnosed with delirium had been in the PICU for a greater number of days at time of assessment (8 d [3, 21] vs. 4 d [2,14], p <0.001). Delirium prevalence varied significantly with reason for ICU admission, with highest delirium rates (42%) found in children admitted with an infectious or inflammatory disorder (Table 2). There was no association between delirium and gender, race, or ethnicity.

In a multivariate model, adjusted odds ratios showed an independent association between development of delirium and age < 2 y, physical restraints, MV, narcotics, benzodiazepines, anti-epileptics, and vasopressors. In this cohort, post-operative patients (those who had received general anesthesia for a surgical procedure within the preceding 24 hours) were less likely to be diagnosed with delirium (Table 3). Delirium prevalence rates increased dramatically after PICU day 5. For children in the ICU for < 6 days, delirium prevalence was 20%. For children who were in the ICU for 6 or more days, delirium prevalence was 38% (p<0.001) (Figure 2).

DISCUSSION

Delirium Prevalence

This large, multi-center study establishes that delirium is a frequent complication of critical illness in childhood, with a point prevalence of 25% across multiple institutions. Our findings are consistent with those of prior single-center studies which reported PD rates ranging from 10–30%(14,15,18,20,25). Children requiring MV (likely with an increased exposure to sedatives and higher severity of illness) had a delirium prevalence of 53%. Although alarmingly high, this is less than the 60–80% reported in adults on MV, perhaps suggesting that the pediatric brain is somewhat protected from delirium development(8,10). The varying prevalence rates of delirium among institutions may reflect different patient populations, varying severity of illness, heterogeneity in prescribing and sedation practices or other unknown factors. A number of these may be amenable to intervention, and could lead to a decrease in PD.

It is interesting to note that we found the highest prevalence of delirium in critically-ill children admitted with infectious/inflammatory disorders. This supports the hypothesis that inflammation plays a leading role in the development of delirium in children. The neuro-inflammatory hypothesis, a prominent etiologic theory for delirium development, posits that systemic inflammation leads to cytokine release with subsequent effects within the central nervous system that are yet undescribed –leading to neuronal and synaptic dysfunction and ultimately clinical symptoms(26,27). Several studies in adults with delirium have shown increases in pro-inflammatory cytokines(28–30), yet a causal relationship in these observational studies has not been proven. It is possible that this finding may relate to perfusion status, rather than inflammation, as these children may have had periods of end-organ hypoperfusion during their PICU stay. Additional work in understanding how the immune system may play a role in delirium pathogenesis – especially in children – appears warranted.

Risk Factors for Delirium

The risk factors for delirium outlined in our large cohort support previous work within the field. Numerous studies of delirium in adults have shown a strong association between development of delirium and both exposure to benzodiazepines and use of physical restraints(31–36). A recent prospective single-center study of PD demonstrated an association between delirium and age less than 5 years, severity of illness, need for MV, and pharmacologic sedation(18). In our study, we found that slightly lower age (< 2 y), MV, and exposure to vasopressor medications (likely a marker for severity of illness) and anti-epileptics (correlating with underlying neurologic issues) were independently associated with increased risk of delirium. Moreover, we also found that benzodiazepines, narcotics, and physical restraints were also strongly associated with delirium. In fact, odds of delirium were four times higher for patients who were physically restrained even after controlling our analysis for MV and sedating medications. This may imply that physically restraining a child increases risk of delirium development, as it does in adults, or it may reflect the fact that children with delirium may require physical restraints in order to maintain necessary medical devices. We cannot assess temporality in this point-prevalence study design(10).

Even with the progress we have made with observational delirium screening, 16% of children were unable to be quickly assessed for delirium. These were children with developmental disabilities, where the bedside caregiver could not clearly establish whether there was an alteration from the child's baseline neurological examination (i.e.: whether the altered awareness and cognition represented acute delirium, or could better be explained by the pre-existing neurologic disorder) (1). A large number of these children may have been delirious, but require a more nuanced approach to tease out the complex interplay between static encephalopathy and delirium(37). This may have artificially lowered the delirium rate measured.

Timing of Delirium

This is the largest pediatric study to systematically determine the timing of delirium and we found that the prevalence of delirium increased with length of time in the PICU. We surmise that this may reflect an accumulation of modifiable iatrogenic risk factors over the course of the illness, and we doubt that it is related to non-modifiable demographic risk factors (such as age, recent surgery, diagnosis on admission, or presence of seizure disorder). However, it is also possible that this reflects those patients with highest severity of illness, whose length of stay is generally longer. As an example, we found decreased delirium rates in children who had received general anesthesia in the previous 24 hours. We believe that this reflects those patients who were recently admitted for recovery after an elective surgical procedure, with lower severity of illness and shorter time spent in the PICU when compared with the larger cohort. Only a longitudinal study to follow children throughout their ICU stay can fully explore how delirium may arise in children with critical illnesses(18). In critically-ill adults, delirium screening occurs in regular intervals based on local standards, usually several times each day. Implementing such a procedure in children – either in research protocols or as part of standard practice – would allow for monitoring of trends within an individual, rather than a one-time snapshot. In this point prevalence study, we were only able to include two time points overall, and only one per patient. We believe that a more comprehensive study may discern seasonal variation (based on disease patterns, or seasonal difference in sunlight) and day/night variation in delirium rates.

Feasibility of Delirium Screening

Importantly, this study demonstrates the practicality of bedside screening using the CAPD. Twenty-five institutions, with varied culture and practices, were all able to complete this tool on the vast majority of their patients without difficulty. The Society of Critical Care Medicine released clinical practice guidelines in January 2013, stating that "monitoring critically ill (adult) patients for delirium with valid and reliable delirium assessment tools enables clinicians to potentially detect and treat delirium sooner, and possibly improve outcomes"(10). We believe this is also true for critically ill children. With implementation of routine pediatric screening, clinicians will be able to detect delirium earlier, which may allow for timely intervention, and optimization of management.

This study has several strengths and important limitations. The multi-institutional nature of the study strongly suggests that delirium is widely prevalent in the overall population of children with critical illnesses. Moreover, the prevalence we observed was strikingly similar

to single-center experiences, providing face validity for both this large study as well as those previously described within the literature. Our cohort represented children with a wide range of pathologies and severity of illness, allowing us to identify risk factors that have not been identified in other studies. Lastly, the study sites were able to determine a delirium status for 84% of the 994 subjects.

With regard to limitations, the CAPD was originally designed to be scored by the nurse at the end of her/his shift – taking advantage of a prolonged observational period to assess the child's neurological performance(16). In our study, the CAPD was administered by the bedside nurse at approximately mid-day so that all of the data could be collected by site coordinators. It is possible that a child may not have demonstrated the fluctuating symptoms of delirium during this time, but went on to develop delirium over the course of the next several hours, after the assessment was complete. Secondly, this study was performed during the day shift and did not account for children who showed signs of delirium at night. As such, we may have underestimated the true PD rate. In addition, although the CAPD detects all forms of delirium, it does not discriminate between them. Therefore, we did not capture delirium subtype (hypoactive, hyperactive, and mixed) in this study; this is an important area for future research. Lastly, we collected a limited amount of data for this study. We believe that this is appropriate for our study design, yet other important covariates including sedation scores, severity of illness scores, and total drug exposure likely play a pivotal role in delirium prevalence and pathophysiology.

CONCLUSION

In this multi-institutional, multi-national point-prevalence study of 994 subjects, delirium screening by the bedside nurse was feasible in children of all ages. Pediatric delirium was a common complication of critical illness, with a prevalence of 25% and identifiable risk factors. Future large scale multi-institutional studies in this field, including longitudinal studies, are warranted to better determine the time course of delirium, understand its burden to childhood health, and its relationship with important clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the support of the WCMC Clinical and Translational Science Center (CTSC GRANT UL1 TR000457) for REDCap and research coordination to collect, analyze, and interpret the data.

FINANCIAL SUPPORT: Weill Cornell Medical College Clinical and Translational Science Center (CTSC GRANT UL1 TR000457) for REDCap and research coordination to collect, manage, analyze, and interpret the data.

Dr. DiGennaro received funding from salary/employment (I am employed full time as a pediatric intensivist at Seattle Children's Hospital with an academic appointment through the University of Washington), speaking fees (I was invited to speak at the American Association of Critical Care Nurses [Portland, Oregon] annual conference in 2013. My hotel was paid for by the AACN, and I additionally received $600 to offset the cost of travel and meals), and from a grant (I received a grant for $50,000 from Seattle Children's Hospital Academic Enrichment Fund for a pilot randomized trial of acupuncture as an adjunct to pharmacologic sedation in mechanically ventilated children). Dr. Cheifetz received funding from Philips and from Ikaria (both unrelated to the topic of the current manuscript).

Dr. Truemper's institution received funding from Gerber Foundation (through University of Nebraska, Lincoln). Dr. O'Meara received funding from Virginia Commonwealth University (salary and internal research grant). Dr. Greenwald received funding from various law firms and insurance companies for expert testimony.

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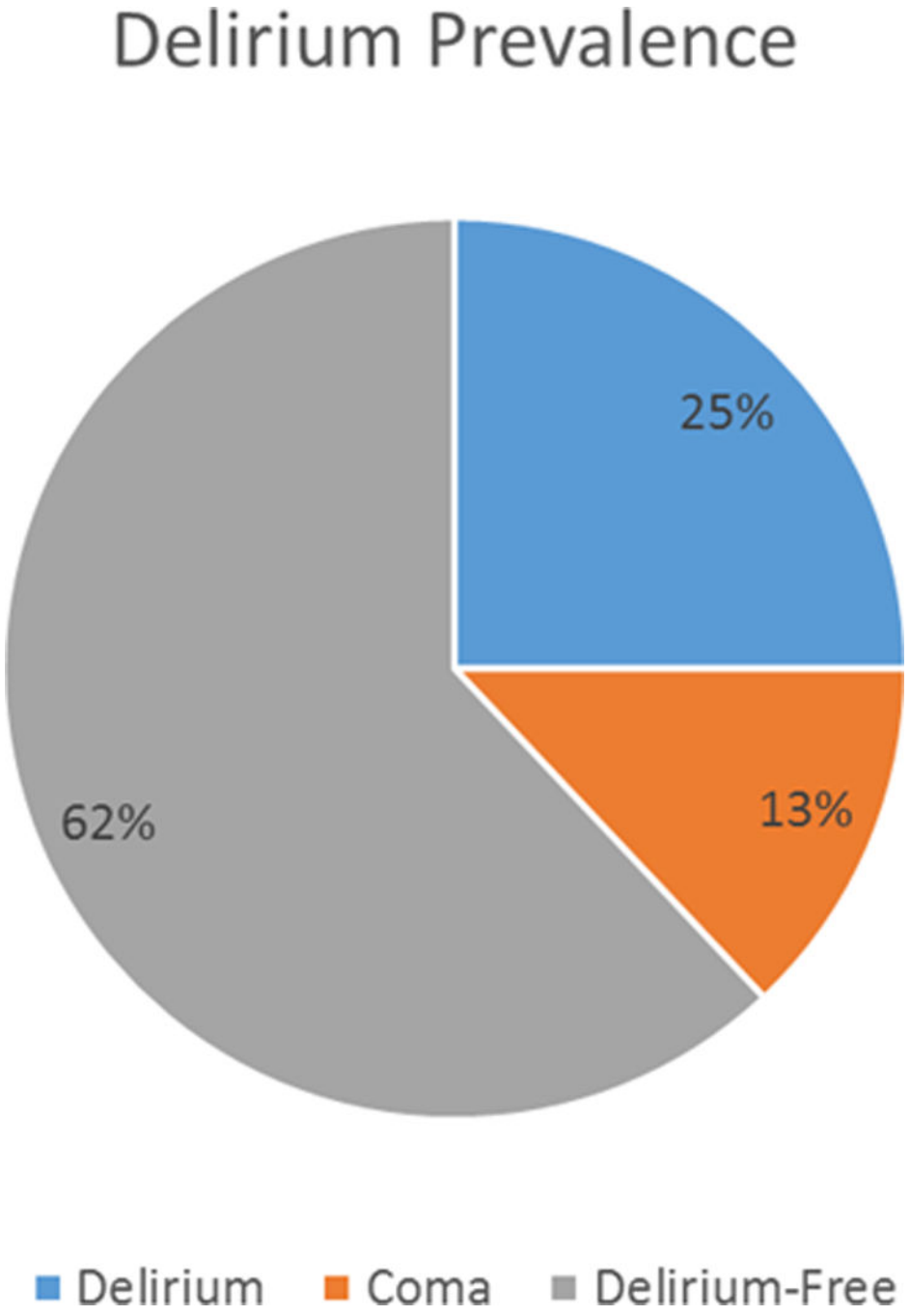

Figure 1. Determination of mental status (n=835)

Delirium defined as CAPD score ≥9. Coma defined as subject unarousable to verbal stimulation. 159 children with developmental delay were excluded from this analysis as the bedside nurse could not establish alteration from neurologic baseline.

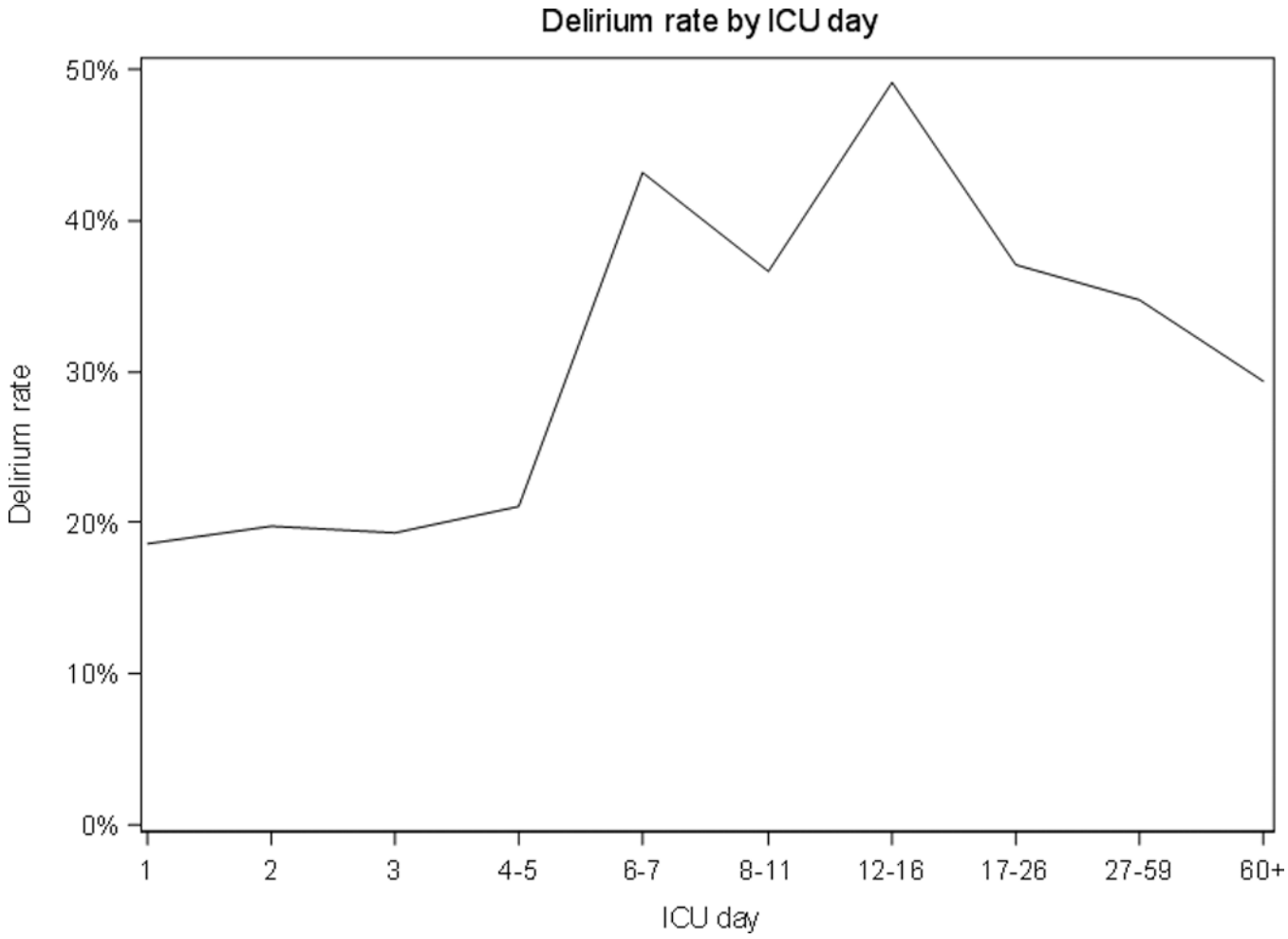

Figure 2. Delirium rate by ICU day

Percentages are based on assessable subjects who were not comatose (n=723). Study days were collapsed to ensure that at least 50 subjects were in each group to prevent an arbitrary variation in delirium rate.

TABLE 1

Description of subjects

	(N = 994)
Reason for ICU Admission	
Cardiac Disease	252 (25.4%)
Hematologic/Oncologic Disorder	49 (4.9%)
Infectious/Inflammatory	67 (6.7%)
Neurologic Disorder	167 (16.8%)
Renal/Metabolic Disorder	44 (4.4%)
Respiratory Insufficiency/Failure	415 (41.8%)
Day of PICU stay Median [Q1, Q3]	6 [2, 19]
Age	
0–2 years	484 (48.7%)
2–5 years	144 (14.5%)
5–13 years	198 (19.9%)
>13 years	167 (16.8%)
Male	537 (54.0%)
Race	
American Indian/Alaska Native	5 (0.5%)
Asian	33 (3.3%)
Black/African American	193 (19.5%)
Native Hawaiian/Pacific Islander	4 (0.4%)
Other	180 (18.2%)
White	574 (58.0%)
Hispanic or Latino	142 (14.5%)
Developmental delay	372 (37.5%)
Invasive mechanical ventilation	355 (35.7%)
Benzodiazepines	427 (43.0%)
Narcotics	543 (54.6%)

Age, race, and ethnicity had 1, 5, and 17 missing values, respectively.

Table 2

Univariate associations

	Delirium		
	No (N = 514)	**Yes (N = 209)**	**P-value**
Reason for ICU Admission			0.017[1]
Cardiac Disease	139 (70.6%)	58 (29.4%)	
Hematologic/Oncologic Disorder	32 (72.7%)	12 (27.3%)	
Infectious/Inflammatory	26 (57.8%)	19 (42.2%)	
Neurologic Disorder	73 (63.5%)	42 (36.5%)	
Renal/Metabolic Disorder	31 (88.6%)	4 (11.4%)	
Respiratory Insufficiency/Failure	213 (74.2%)	74 (25.8%)	
Day of PICU stay Median [Q1, Q3]	4.0 [2.0, 14.0]	8.0 [3.0, 21.0]	<.001[2]
≤ 2 years	236 (67.6%)	113 (32.4%)	0.049[1]
Physical restraints	16 (27.6%)	42 (72.4%)	<.001[1]
Mechanical ventilation	92 (47.4%)	102 (52.6%)	<.001[1]
Non-invasive ventilation	53 (67.9%)	25 (32.1%)	0.511[1]
High flow nasal cannula	52 (73.2%)	19 (26.8%)	0.783[1]
Supplemental oxygen	88 (75.9%)	28 (24.1%)	0.263[1]
Narcotics	231 (59.7%)	156 (40.3%)	<.001[1]
Benzodiazepines	136 (52.7%)	122 (47.3%)	<.001[1]
Dexmedetomidine *	33 (62.3%)	20 (37.7%)	0.157[1]
Antipsychotics	17 (63.0%)	10 (37.0%)	0.387[1]
Antiepileptics	59 (52.2%)	54 (47.8%)	<.001[1]
General anesthesia	86 (78.9%)	23 (21.1%)	0.052[1]
Vasopressors	61 (50.4%)	60 (49.6%)	<.001[1]
Anticholinergics	182 (68.4%)	84 (31.6%)	0.235[1]
Systemic steroids	159 (65.2%)	85 (34.8%)	0.015[1]

Percentages reported are by rows. P-values were calculated by Fisher's exact test[1] and Wicoxon rank-sum test[2].

Race and ethnicity had 4 and 14 missing values respectively.
Respiratory support categories are mutually exclusive; highest level of respiratory support was captured.

* Dexmedetomidine as sole sedative, without benzodiazepines.

Table 3

Multivariate associations with delirium

Variable	Adjusted odds ratios (95% CI)
Age > 2 years	0.7 (0.5, 1.0)
Physical restraints	4.0 (2.0, 7.7)
Mechanical ventilation	1.7 (1.1, 2.7)
Narcotics	2.3 (1.5, 3.5)
Benzodiazepines	2.2 (1.5, 3.3)
Antiepileptics	2.9 (1.8, 4.8)
General anesthesia	0.4 (0.3, 0.8)
Vasopressors	2.4 (1.5, 3.8)