Delirium and Benzodiazepines Associated With Prolonged ICU Stay in Critically Ill Infants and Young Children*

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Objectives: Delirium is prevalent among critically ill children, yet associated outcomes and modifiable risk factors are not well defined. The objective of this study was to determine associations between pediatric delirium and modifiable risk factors such as benzodiazepine exposure and short-term outcomes.

Design: Secondary analysis of collected data from the prospective validation study of the Preschool Confusion Assessment Method for the ICU.

Setting: Tertiary-level PICU.

Patients: Critically ill patients 6 months to 5 years old.

Interventions: None.

Measurements and Main Results: Daily delirium assessments were completed using the Preschool Confusion Assessment Method for the ICU. Associations between baseline and inhospital risk factors were analyzed for likelihood of ICU discharge using Cox proportional hazards regression and delirium duration using negative binomial regression. Multinomial logistic regression was used to determine associations between daily risk factors and delirium presence the following day. Our 300-patient cohort had a median (interquartile range) age of 20 months (11–37 mo), and 44% had delirium for at least 1 day (1–2 d). Delirium was significantly associated with a decreased likelihood of ICU discharge in preschool-aged children (age-specific hazard ratios at 60, 36, and 12 mo old were 0.17 [95% CI, 0.05–0.61], 0.50 [0.32–0.80], and 0.98 [0.68–1.41], respectively). Greater benzodiazepine exposure (75–25th percentile) was significantly associated with a lower likelihood of ICU discharge (hazard ratio, 0.65 [0.42–1.00]; p = 0.01), longer delirium duration (incidence rate ratio, 2.47 [1.36–4.49]; p = 0.005), and increased risk for delirium the following day (odds ratio, 2.83 [1.27–6.59]; p = 0.02).

Conclusions: Delirium is associated with a lower likelihood of ICU discharge in preschool-aged children. Benzodiazepine exposure is associated with the development and longer duration of delirium, and lower likelihood of ICU discharge. These findings advocate for future studies targeting modifiable risk factors, such...
Pediatric delirium is a syndrome of acute brain dysfunction that is highly prevalent among the critically ill, with rates of up to 30% in older children (1–4) and over 50% in infants and toddlers (5). The creation of highly valid and reliable pediatric delirium tools has made delirium screening and monitoring in the PICU setting not only practical (1, 2, 5, 6) but provides the means to further understand the impact of delirium in our most fragile population. In critically ill adults, delirium has been associated with poorer outcomes including prolonged ICU and hospital length of stay (LOS), long-term cognitive impairment (LTCI), and even death (7–9). Small cohort studies in critically ill children have demonstrated similar associations between delirium and longer ICU stay and higher costs (10, 11), whereas a recent point prevalence study on delirium reported associated risk factors to include age, mechanical ventilation, benzodiazepines, opioids, use of physical restraints, and exposure to vasopressors and antiepileptics (4). The etiology of delirium can be multifactorial, with the end result being a disruption of the fragile balance between excitatory and inhibitory neurotransmission (12). This imbalance manifests through characteristic behaviors that are commonly observed and can range from hyperactivity and agitation to a patient appearing withdrawn and sedate (13, 14).

Delirium risk factors have been well delineated in adults to include iatrogenic factors such as immobilization, sleep deprivation, and a strong association with benzodiazepine exposure (15–19). The iatrogenic harm resulting from benzodiazepine use in adults has been consistently demonstrated to include greater development and duration of delirium, increased duration of mechanical ventilation, and longer ICU and hospital LOS (20–22). This realization is pertinent as up to 90% of mechanically ventilated infants and children receive continuous sedation (23), commonly centered around the use of high-dose midazolam for multiple days (24, 25). In fact, high-dose oral benzodiazepines have been associated with paradoxical agitation, and thus, it is plausible that high-dose IV benzodiazepines, frequently administered to critically ill patients, could predispose patients to delirium (26).

Thus, the hypothesis for this large prospective study is that delirium is associated with worse clinical outcomes among critically ill infants and young children and that routine sedation protocols using benzodiazepines predispose patients to delirium.

**MATERIALS AND METHODS**

We conducted a prospective observational study of pediatric patients, 6 months to 5 years old admitted to the PICU at Monroe Carell Jr. Children’s Hospital at Vanderbilt regardless of diagnosis, for the following purposes: 1) to validate an objective delirium tool for critically ill infants and young children and 2) to determine associated risk factors and outcomes for delirium. The reliability and validity of the Preschool Confusion Assessment Method of the ICU (psCAM-ICU) for delirium monitoring in infants and young children have previously been published in *Critical Care Medicine* (5). The data regarding delirium risk factors and outcomes presented in this article have not been previously published. Exclusion criterion for this study included the following: hearing/visual impairments, cognitive development less than expected for 6 months old, non-English speaking, planned PICU discharge/transfer, moribund, or for whom consent could not be obtained. The institutional review board approved this study. We assessed patients daily for delirium for up to 14 days or until transfer/discharge from the PICU, whichever came first. Delirium assessments were conducted only once daily due to restricted availability of research personnel for purposes of the validation study.

Baseline demographics and data pertaining to predisposing risk factors for delirium were collected upon admission including age, history of cyanotic cardiac disease, severity of illness (Pediatric Risk of Mortality III [PRISM III] score), and admission diagnosis. Additionally, information was collected regarding in-hospital risk factors which may contribute to the development and/or duration of delirium. These data included benzodiazepine and opioid exposures, cardiovascular Sequential Organ Failure Assessment (SOFA) score, need for mechanical ventilation, and presence of hypoxia. In patients with cyanotic heart disease, we defined hypoxia as oxygen saturations less than 75% or less than the patient’s baseline saturations. Outcome data on both ICU and hospital LOS were also monitored and recorded. PRISM III is a severity of illness score that is calculated using the most abnormal variables during the 24 hours prior to and including admission to the PICU. PRISM scores range from 0 (best) to 30 (worst) (27). The cardiovascular SOFA score reflects degree of cardiovascular dysfunction in critically ill children, with a range from 0 (best) to 4 (worst), based on amount of vasopressor or inotropic support required. The cardiovascular SOFA is part of the modified SOFA score that has been shown to predict morbidity and mortality in critically ill children (28).

Each day, patients were classified as either having “coma, delirium, or normal mental status.” Level of arousal was first determined using a sedation scale, in this case, the Richmond Agitation Sedation Scale (RASS) (29). Patients who had a greatly decreased level of arousal to include either a RASS ≤ –4 or –5 were categorized as having “coma” and therefore were not assessed for delirium at that time, rather reassessed the following day. Patients who were spontaneously awake or aroused by voice (RASS ≥ –3) underwent delirium assessment (content of consciousness) using the psCAM-ICU. The psCAM-ICU is a highly valid and reliable bedside tool used by healthcare providers for delirium diagnosis in critically ill infants and young children (specificity, 91%; sensitivity, 75%; and κ, 0.79) (5). The psCAM-ICU assesses for key features of delirium: acute
alteration or fluctuation from baseline mental status (feature 1), inattention (feature 2), acute alteration of consciousness (feature 3), and dysregulation of cognition/systems (feature 4). For “delirium” diagnosis using the psCAM-ICU, a patient must have a RASS score greater than or equal to –3 and demonstrate having features 1 and 2, plus either feature 3 or 4. A patient with a RASS greater than or equal to –3 without delirium was considered “normal.”

Patient characteristics including demographics, admission diagnoses, the PICU clinical course, and outcomes were summarized using frequencies (%) for categorical variables and medians and interquartile ranges (IQRs) for continuous variables.

Multivariable Cox proportional hazard models were used to determine the associations between mental status (delirium, coma, or normal) and other a priori chosen risk factors (age, severity of illness, admission diagnosis of sepsis or acute respiratory distress syndrome [ARDS], cyanotic heart disease, benzodiazepine exposure, opiate exposure, dexmedetomidine exposure, cardiovascular SOFA score, and hypoxia) on the likelihood of ICU discharge. The hazard ratios (HRs) represent the chance of an event, or in these models, the likelihood of ICU discharge on a given day. A HR greater than one is positive or desirable as it correlates with a “greater likelihood” of ICU discharge on a given day and therefore a shorter LOS. Conversely, a HR less than one is negative or less desirable as it pertains to a “lower likelihood” of ICU discharge on a given day. All continuous variables were originally allowed to have a nonlinear relationship with outcomes using restricted cubic splines. If these nonlinear and/or interaction terms were clearly nonsignificant (p > 0.20) in a given model, they were removed from the final version in order to make interpretation and explanations as straightforward as possible. In other words, all covariates remained in the model as specified a priori; however, the level of complexity for the associations between covariates and the outcome was allowed to change. In all models, drug doses were converted using the cube root transformation in order to mitigate the influence of extremely high values.

We used negative binomial regression to determine the associations between delirium duration and both baseline and day 1 in-hospital risk factors (age, severity of illness, admission diagnosis of sepsis or ARDS, cyanotic heart disease, benzodiazepine and opiate exposures, cardiovascular SOFA score, mechanical ventilation, and hypoxia) that were present prior to the first delirium assessment. The outcome measure of delirium duration was the sum of daily positive delirium screenings for an individual patient, with up to 14 daily assessments or less if transfer/discharge from the PICU occurred prior to 14 days.

Finally, multinomial logistic regression was used to determine the role of risk factors (age, daily exposure to benzodiazepines and opioids, mechanical ventilation, cardiovascular SOFA score, and hypoxia) on mental status (normal, delirious, or comatose) from 1 day to the next. For purposes of this analysis, the outcome variable was the daily mental status assignments across the entire cohort. Since multiple daily assessments could be used from each hospitalization in this model, we used bootstrapping clustered by patient to adjust the SES and account for correlation among assessments from the same patient.

All analyses were performed using R-statistical software version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). We graphically assessed the proportional hazard assumption for time-to-event model(s); these assumptions were met satisfactorily.

RESULTS

Three hundred patients were enrolled from March 2013 to October 2014. A total of 320 patients were consented, however, 20 patients did not complete the study due to unavailability of research personnel (12 subjects) or baseline developmental delay (eight subjects). Demographic and summary data are presented in Table 1. We previously reported the prevalence of delirium in this cohort of 44%, with rates of delirium as high as 53% in patients less than or equal to 2 years old and 33% in patients between 2–5 years of age (5). The median (IQR) duration of delirium was 1 day (1–2 d).

Nonnormal mental status (delirium or coma) had a meaningful association with a lower likelihood of ICU discharge on a given day (p = 0.051) (Table 2). The different HRs presented for delirium and coma further describe their individual associations with likelihood of ICU discharge when compared with having a normal mental status. Since this association was greatly modified by age, the above single p value cannot fully describe the depth of the relationship between mental status and likelihood of ICU discharge. Rather, Figure 1 is necessary to illustrate the significant associations between delirium and lower likelihood of ICU discharge among preschool-aged children (> 12 mo old). Benzodiazepine exposure was also significantly associated with a lower likelihood of ICU discharge (p = 0.01). Other risk factors significantly associated with a lower likelihood of ICU discharge included younger age (p = 0.01) and hypoxia (p < 0.001). In contrast, dexmedetomidine exposure increased the likelihood of ICU discharge (p = 0.008), therefore more likely associated with a shorter LOS. The aforementioned relationships were nonlinear; therefore, the HRs presented in Table 2 are specific for the comparison of the 75th to 25th percentiles of each risk factor for likelihood of ICU discharge.

An increase in delirium duration was significantly associated with higher benzodiazepine exposure (p = 0.005). Additionally, younger age (p = 0.005) and higher severity of illness (p = 0.007) were also predictors of longer delirium duration. (Table 3) The aforementioned relationships were nonlinear; therefore, the incidence rate ratios (IRRs) presented in Table 3 are specific for the comparison of the 75th to the 25th percentiles of all risk factors assessed. As an example, when considering benzodiazepine exposure, the 75th and 25th percentiles in our cohort were 0.73 and 0 mg/kg/d, respectively, on the day prior to the first delirium assessment. The IRR of 2.47 (95% CI, 1.36–4.49) indicates that, on average, a patient receiving 0.73 mg/kg/d of benzodiazepine will have about 2.5 times the incidence rate of delirium compared with a patient...
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Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/C656; legend, Supplemental Digital Content 2, http://links.lww.com/CCM/C657) further illustrates the depth of these significant associations.

Benzodiazepine exposure was the sole independent predictor for the development of delirium the day following exposure compared with having a normal mental status ($p = 0.02$). (Fig. 2) As an illustration, an odds ratio of 2.83 for this relationship means that patients, with approximately 1 mg/kg of benzodiazepine exposure when compared with 0 mg (the 75th and 25th percentiles benzodiazepine exposure) in a 24-hour period, have 2.8 times the odds of developing delirium the following day versus having a normal mental status. There was no statistically significant relationship between age, opioid exposure, mechanical ventilation, or cardiovascular SOFA score on the development of delirium the following day.

**DISCUSSION**

In this large prospective cohort study, four of 10 children suffered from delirium during their ICU stay. Delirium and benzodiazepine exposures were significantly associated with a lower likelihood of ICU discharge. Patients who were exposed to greater amounts of benzodiazepine suffered from a considerably longer delirium duration. Furthermore, patients with high benzodiazepine exposure were significantly more likely to develop delirium the day following the exposure when compared with those with minimal or no exposure. The importance of high delirium rates during critical illness is highlighted by the significant observations of prolonged ICU LOS in this study and prior reports, in addition to previously described higher associated costs (10, 11). With benzodiazepine use being associated with not only prolonged delirium duration but also a lower likelihood of ICU discharge, there is now a potentially modifiable risk factor to target for interventional trials aimed at improving pediatric outcomes following critical illness.

Delirium during critical illness was a significant predictor of a lower likelihood of ICU discharge among preschool-aged children (> 12 mo old). This finding may be a reflection of severity of illness; as many of the infants and toddlers in our study were patients admitted following cardiac surgery and had more comorbidities and a higher severity of illness. So, delirium in this setting may have had a smaller impact on the likelihood of ICU discharge when compared with other significant elements of critical illness among these patients. Previous studies have demonstrated that severity of illness scores may be useful for predicting delirium in the PICU, though this relationship may be influenced by other factors of the critical illness as well (30).

Additionally, it is possible that delirium was not routinely recognized by the medical team among the youngest patients and therefore not considered in the decision-making for ICU discharge, where an abnormal mental status is more commonly alarming among older, normally interactive patients.

**TABLE 1. Demographics and Baseline and Summary Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (n = 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age at enrollment (mo), median (IQR)</td>
<td>20 (11–37)</td>
</tr>
<tr>
<td>Sex, frequency (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>112 (37)</td>
</tr>
<tr>
<td>Male</td>
<td>188 (63)</td>
</tr>
<tr>
<td>Race, frequency (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>60 (20)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>229 (76)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>11 (8–14)</td>
</tr>
<tr>
<td>Baseline and in-hospital variables</td>
<td></td>
</tr>
<tr>
<td>Cyanotic heart disease, frequency (%)</td>
<td>91 (30)</td>
</tr>
<tr>
<td>Pediatric Risk of Mortality score (day 1), median (IQR)</td>
<td>5 (0–10)</td>
</tr>
<tr>
<td>Sepsis or related admission disease, frequency (%)</td>
<td>112 (37)</td>
</tr>
<tr>
<td>Daily benzodiazepines (midazolam equivalents) (mg/kg), median (IQR)</td>
<td>0.15 (0–1.06)</td>
</tr>
<tr>
<td>Daily opioids (fentanyl equivalents) (µg/kg), median (IQR)</td>
<td>6.3 (0–34.3)</td>
</tr>
<tr>
<td>Daily dexmedetomidine (µg/kg), median (IQR)</td>
<td>0 (0–50)</td>
</tr>
<tr>
<td>Daily cardiovascular Sequential Organ Failure Assessment score, median (IQR)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Daily lowest oxygen saturations, median (IQR)</td>
<td>90 (75–94)</td>
</tr>
<tr>
<td>Summary variables</td>
<td></td>
</tr>
<tr>
<td>Received mechanical ventilation during hospitalization, frequency (%)</td>
<td>130 (43)</td>
</tr>
<tr>
<td>Length of mechanical ventilation (d), median (IQR)</td>
<td>3 (1–5)</td>
</tr>
<tr>
<td>Delirium prevalence (Preschool Confusion Assessment Method of the ICU), frequency (%)</td>
<td>124 (44)</td>
</tr>
<tr>
<td>Duration of delirium among those exposed (d), median (IQR)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Length of ICU stay (d), median (IQR)</td>
<td>4 (3–9)</td>
</tr>
<tr>
<td>Length of hospitalization (d), median (IQR)</td>
<td>8 (4–17)</td>
</tr>
<tr>
<td>In-hospital mortality, frequency (%)</td>
<td>10 (3)</td>
</tr>
</tbody>
</table>

IQR = interquartile range.
Nevertheless, both sedation and delirium are not inconsequential in critically ill children and result in tangible worse clinical outcomes that may come with a cost. Our results begin to parallel prior adult studies that demonstrate a relationship between delirium and longer ICU and hospital LOS.

Understanding the relationships between benzodiazepine administration and delirium are imperative, given that upwards of 90% of critically ill infants and children receive continuous sedation while on mechanical ventilation. Although the use of sedation may be unavoidable in the PICU setting, it remains a modifiable risk factor, where attention to limiting total exposure and considering alternative sedation paradigms may lead to improved patient outcomes. These data are in line with studies of adults where benzodiazepine administration has been shown to be associated with delirium leading to investigations targeting the reduction of sedation, daily interruption of sedation, and the consideration of non-benzodiazepine agents as first line of therapy (15, 31).

The Pain Agitation Delirium guidelines from the Society of Critical Care Medicine (SCCM) (32, 33) and the SCCM ICU Liberation collaborative have both stressed the importance of limiting sedative exposure, and our data in children underscore the importance of such an approach in our most vulnerable patients. This will no doubt challenge the mainstay of care for critically ill children who are usually heavily sedated, with the belief among ICU caregivers that a heavily sedated pediatric patient may be psychologically “saved from the ICU experience.” However, we know that a third of pediatric patients report delusional memories of their ICU experience, associated with longer benzodiazepine and opioid exposure during critical illness, and subsequent reports of higher posttraumatic stress disorder scores following discharge to home (34). We propose transition to the mindset that for every child, every day there is a goal of being alert and calm, while being mindful of clinical goals and the treatment of pain, and thus liberate children more quickly from sedation, mechanical ventilation, and the ICU environment.

In addition to recognizing potentially modifiable risk factors for all patients, identifying baseline risk factors can help pinpoint patients who may benefit from preventive care and perhaps increased vigilance. In this study, infants and younger children and patients with a higher severity of illness were more likely to suffer a longer duration of delirium. A significant association was not demonstrated between delirium duration and presence of cyanotic heart disease, admission diagnosis of sepsis, need for mechanical ventilation, or cardiovascular SOFA score in this cohort. The lack of an independent association between delirium and need for mechanical ventilation, we believe, is due to adjusting for other factors such as severity of illness, hypoxia, and sedative exposure. In other words, this highlights that concurrent use of sedation in patients while on mechanical ventilation assumes a greater association with delirium, rather than the requirement of mechanical ventilation alone. Whereas predisposing risk factors such as age, severity of illness, and baseline developmental delay have been previously demonstrated to be significantly associated with delirium in smaller prospective cohort studies (30, 35), these findings may highlight the importance of the interplay between predisposing and precipitating factors, such that the critical illness alone may not always determine the rate of development or severity of delirium.

The developing brain has been the focus of numerous recent studies that demonstrate the following: 1) pharmacologic action

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**TABLE 2. Risk Factors for Likelihood of ICU Discharge**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Comparison</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (mo)</td>
<td>31 vs 9</td>
<td>1.85 (1.23–2.77)</td>
<td>0.010</td>
</tr>
<tr>
<td>Pediatric Risk of Mortality score at ICU admission</td>
<td>13 vs 0.25</td>
<td>1.21 (0.87–1.68)</td>
<td>0.074</td>
</tr>
<tr>
<td>Sepsis or related diagnosis at ICU admission</td>
<td>Yes vs no</td>
<td>0.99 (0.77–1.29)</td>
<td>0.969</td>
</tr>
<tr>
<td>Benzodiazepines (mg/kg/d)</td>
<td>1 vs 0</td>
<td>0.65 (0.42–1.00)</td>
<td>0.011</td>
</tr>
<tr>
<td>Opioids (µg/kg/d)</td>
<td>3.26 vs 0</td>
<td>0.62 (0.39–0.98)</td>
<td>0.112</td>
</tr>
<tr>
<td>Dexmedetomidine (µg/kg/d)</td>
<td>3.74 vs 0</td>
<td>1.82 (1.25–2.66)</td>
<td>0.008</td>
</tr>
<tr>
<td>Lowest O₂ saturations (%)</td>
<td>94 vs 75</td>
<td>2.18 (1.63–2.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental status</td>
<td>Delirious vs normal</td>
<td>0.94 (0.65–1.36)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Comatose vs normal</td>
<td>0.74 (0.41–1.34)</td>
<td></td>
</tr>
</tbody>
</table>

*The hazard ratio (HR), 95% CI, and p values for likelihood of ICU discharge on a given day are presented for each potential risk factor. A HR > 1 refers to a “greater” likelihood of ICU discharge. Conversely, a HR < 1 refers to a “lower” likelihood of ICU discharge. The p values reflect the entire association for a given covariate magnitude comparison. For continuous covariates, the HRs represent the association between likelihood of discharge at the 75th vs the 25th percentile of each risk factor.

*Drug dosage amounts (mg/kg) were transformed using the cube root transformation in order to mitigate the influence of extremely high values.

*HRs describe the individual associations of delirium and coma vs normal mental status. As the multivariable model allowed for an interaction between age and mental status, Figure 1 is necessary to illustrate the significant relationship between delirium and a lower likelihood of ICU discharge in older children (>12 mo old).
Comatose vs Normal

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Figure 1. Delirium and likelihood of ICU discharge modified by age. Delirium was associated with a lower likelihood of ICU discharge (overall p for mental status = 0.05). This relationship was modified by age (interaction p = 0.10) whereby delirium significantly lowered the likelihood of ICU discharge in preschool-aged patients (>12 mo old). The hazard ratios for likelihood of ICU discharge at 60, 36, and 12 months old were 0.17 (95% CI, 0.05–0.61), 0.50 (0.32–0.80), and 0.98 (0.68–1.41), respectively.

Delirious vs Normal

Delirium was associated with a lower likelihood of ICU discharge (overall p for mental status = 0.05). This relationship was modified by age (interaction p = 0.10) whereby delirium significantly lowered the likelihood of ICU discharge in preschool-aged patients (>12 mo old). The hazard ratios for likelihood of ICU discharge at 60, 36, and 12 months old were 0.17 (95% CI, 0.05–0.61), 0.50 (0.32–0.80), and 0.98 (0.68–1.41), respectively.

at the N-methyl-D-aspartate and gamma-aminobutyric acid receptors produces profound apoptotic and other neurodegenerative changes in the developing brain; 2) multiple exposures to drug/anesthetic administration are associated with adverse cognitive effects controlling for comorbidities; and 3) specific deficits in speech and language have been repetitively identified following drug/anesthetic administration (36–45). Recently, significant declines in both global cognitive and executive functions were associated with longer duration of delirium in adults a year following discharge to home (11). With the current appreciation of the biological development of the immature brain, the interplay between acute and long-term cognitive dysfunction in pediatric patients will be paramount. To this end, the neuropsychiatric and cognitive outcomes associated with acute brain dysfunction should now become the focus.

Several limitations of this prospective study warrant discussion. This study was conducted in critically ill patients 6 months to 5 years old for the following reasons: 1) to validate the psCAM-ICU and 2) to determine risk factors and outcomes associated with pediatric delirium; thus, these results may not be generalizable to older children. However, a recent study on the point prevalence of delirium in critically ill children identified similar associated risk factors (4). Delirium assessments were conducted once daily on enrolled patients until ICU transfer/discharge or for a maximum of 14 days, whichever came first. When a delirium assessment was not available (such as a weekend day), we categorized the assessment as nondelirious. The only outcome measure that depended on the aforementioned reconciliation of missing data was delirium duration. The potential effect on measured results using missing data reconciliation would have been an underestimation of the prevalence and duration of delirium, in other words, a bias toward the null hypothesis. Although over 90% of the study cohort had a PICU LOS less than or equal to 14 days, it is possible that a very small minority of patients, who remained in the ICU longer than the reported 14-day study period, could have suffered a longer duration or later development of delirium. For outcomes such as ICU and hospital LOS, we used exact dates of discharge obtained from the medical record and thus these outcomes were not curtailed at 14 days.

Our primary model determining the association between delirium and benzodiazepine exposure included all patient days with available mental status but did not adjust for the prior day mental status. Adjusting for prior mental status would have required all patients to have 2 consecutive days of mental status assessments, when in fact, there were patients who did not (short ICU LOS or weekend day). If we had adjusted for prior mental status, these patients would have had to be excluded. Rather, we conducted a sensitivity analysis on a subset of patients who had 2 consecutive days of mental status with adjustment for mental status from the previous day. Our findings remained consistent, and benzodiazepine exposure was independently associated with delirium the next day.

Although we included numerous covariates that were deemed clinically relevant a priori, this list was not all-inclusive, and therefore, it is possible that other essential covariates were not measured. Possible iatrogenic risk factors such as sleep deprivation, limited social interactions, and immobility were not included in this study, though clearly, they may play a significant role in delirium duration and hence other important outcomes. Psychoactive drug exposure was a key covariate in this study. However, the relationship between delirium and drug exposure was limited to the dose administered, rather than serum levels. Since drug exposure based solely on dose may disguise the role that renal and hepatic function play in the metabolism and excretion of drugs, the relationships between drug exposure and delirium and other outcomes may be elucidated with the addition of drug serum level surveillance. In order to further elucidate the temporal relationships between delirium and associated risk factors, future studies may benefit from more frequent delirium assessments and sampling of key risk factor–related events.

Finally, this study was not designed to determine the role of delirium in the development of LTCI in children. The current
TABLE 3. Risk Factors for Delirium Duration\textsuperscript{a}

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Comparison</th>
<th>Incidence Rate Ratio (95% CI)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (mo)\textsuperscript{b}</td>
<td>37 vs 11</td>
<td>0.51 (0.35–0.76)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cyanotic heart disease</td>
<td>Yes vs no</td>
<td>1.23 (0.72–2.10)</td>
<td>0.477</td>
</tr>
<tr>
<td>Pediatric Risk of Mortality score at enrollment\textsuperscript{b}</td>
<td>10 vs 0</td>
<td>2.25 (1.28–3.94)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sepsis or related condition at ICU admission</td>
<td>Yes vs no</td>
<td>1.05 (0.69–1.59)</td>
<td>0.823</td>
</tr>
<tr>
<td>Benzodiazepines (mg/kg/d)\textsuperscript{b,c}</td>
<td>0.73 vs 0</td>
<td>2.47 (1.36–4.49)</td>
<td>0.005</td>
</tr>
<tr>
<td>Opioids ((\mu)g/kg/d)\textsuperscript{c}</td>
<td>3.3 vs 0</td>
<td>0.70 (0.33–1.48)</td>
<td>0.410</td>
</tr>
<tr>
<td>Cardiovascular Sequential Organ Failure Assessment score</td>
<td>1 vs 0</td>
<td>0.96 (0.79–1.17)</td>
<td>0.691</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Yes vs no</td>
<td>0.66 (0.37–1.16)</td>
<td>0.135</td>
</tr>
<tr>
<td>Lowest (O_2) saturations</td>
<td>95 vs 87</td>
<td>1.03 (0.67–1.59)</td>
<td>0.516</td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\) All continuous covariates had nonlinear associations with delirium duration, and as such, a single-point estimate does not fully describe the relationship. To more precisely understand this association, the incidence rate ratios (IRR), 95\% CI, and \(p\) values represent the comparative association for each potential risk factor and delirium duration. These comparative examples use values corresponding with the 75th and 25th percentiles for continuous variables, and therefore, the IRRs represent only these comparative associations.

\(\textsuperscript{b}\) Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/C656; legend, Supplemental Digital Content 2, http://links.lww.com/CCM/C657) further illustrates the depth of these nonlinear associations between age, Pediatric Risk of Mortality scores, and benzodiazepine exposure with delirium duration.

\(\textsuperscript{c}\) Drug dosage amounts (mg/kg) were transformed using the cube root transformation in order to mitigate the influence of extremely high values.

Figure 2. Benzodiazepine exposure versus mental status the following day. We examined the relationships between potential risk factors and mental status the following day using multinomial regression. Drug dosage amounts (mg/kg) were transformed using the cube root transformation in order to mitigate the influence of extremely high values. After adjusting to the median or mode of all other covariates, higher benzodiazepine doses were significantly associated with a higher likelihood of being delirious compared with having a normal mental status (\(p = 0.02\)) the day following the exposure.
evidence for a relationship between delirium and LTCI in adults bolsters the need for further study in pediatric patients, who are undergoing a steep trajectory of neurodevelopment prior to their interceding critical illness.

CONCLUSIONS

In this large prospective cohort study of critically ill infants and young children, delirium and greater benzodiazepine exposures were associated with a lower likelihood of ICU discharge. This is an important finding as delirium occurs in four of 10 critically ill infants and younger children. Hence, interventional trials are necessary to determine whether reducing iatrogenic harm through the optimization of benzodiazepine exposure decreases the burden of pediatric delirium and improves clinical outcomes in children.

REFERENCES