A Systematic Review and Pooled Prevalence of Delirium in Critically Ill Children

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OBJECTIVES: Pediatric delirium is a neuropsychiatric disorder with disrupted cerebral functioning due to underlying disease and/or critical care treatment. Pediatric delirium can be classified as hypoactive, hyperactive, and mixed. This systematic review was conducted to estimate the pooled prevalence of pediatric delirium using validated assessment tools in children (Cornell Assessment of Pediatric Delirium, Pediatric Confusion Assessment Method for the ICU, PreSchool Confusion Assessment Method for the ICU, Pediatric Confusion Assessment Method for the ICU Severity Scale, and Sophia Observation Withdrawal Symptoms Pediatric Delirium scale), identify modifiable and nonmodifiable risk factors, and explore the association of pediatric delirium with clinical outcomes.

DATA SOURCES: A systematic search of PubMed, EMBASE, and CINAHL databases was undertaken for full articles pertaining to pediatric delirium prevalence.

STUDY SELECTION: No language or date barriers were set. Studies were included where the following eligibility criteria were met: study design aimed to estimate pediatric delirium prevalence arising from treatment in the intensive care setting, using a validated tool. Only randomized controlled trials, cross-sectional studies, or cohort studies allowing an estimate of the prevalence of pediatric delirium were included.

DATA EXTRACTION: Data were extracted by the primary researcher (D.S.) and accuracy checked by coauthors.

DATA SYNTHESIS: A narrative synthesis and pooled prevalence meta-analysis were undertaken.

CONCLUSIONS: Pediatric delirium, as determined by the Cornell Assessment of Pediatric Delirium score, is estimated to occur in 34% of critical care admissions. Eight of 11 studies reporting on subtype identified hypoactive delirium as most prevalent (46–81%) with each of the three remaining reporting either hyperactive (44%), mixed (57%), or equal percentages of hypoactive and mixed delirium (43%) as most prevalent. The development of pediatric delirium is associated with cumulative doses of benzodiazepines, opioids, the number of sedative classes used, deep sedation, and cardiothoracic surgery. Increased time mechanically ventilated, length of stay, mortality, healthcare costs, and associations with decreased quality of life after discharge were also found. Multi-institutional and longitudinal studies are required to better determine the natural history, true prevalence, long-term outcomes, management strategies, and financial implications of pediatric delirium.

KEY WORDS: critical illness; delirium; hypnotics and sedatives; intensive care units; pediatrics; risk factors

Delirium is a neuropsychiatric disorder with disrupted cerebral functioning due to underlying disease and/or as a result of critical care treatment (1, 2). Patients fluctuate between hypoactive (decreased responsiveness/withdrawal), hyperactive (agitation/restlessness), and mixed (combined) clinical states (2, 3). Phenotypes of delirium are classified by psychiatric evaluation

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and using the Richmond Agitation-Sedation Scale (4–6). A score of –3 to –1 indicates hypoactive and +1 to +4 hyperactive, with fluctuations between negative and positive values indicating mixed pediatric delirium (PD) (6). Hypoactive delirium might be more accurately described as "acute apathy syndrome," in part due to differences in management and outcomes (7, 8). Delirium in critically ill children is associated with displacement of essential hardware (e.g., central venous access devices, endotracheal tubes), prolongation of mechanical ventilation (MV) and length of stay (LOS), increased healthcare costs, and mortality (3).

PD if at all recognized has been historically underdiagnosed or misdiagnosed (3, 9–11). Difficulties in diagnosis include the varying terms to describe it: ICU syndrome, acute confusion state, acute brain failure, septic encephalopathy, and a differential that includes infection, iatrogenic withdrawal syndrome (IWS), neurologic trauma, pain, and discomfort—reflected by the acronym IWATCHDEATH (Infection, Withdrawal, Acute metabolic Trauma, Hypoxia, Deficiencies, Environmental, Acute Vascular Toxins/drugs, Heavy metals) (12–14). Traditionally, PD was identified by psychiatric evaluation using Diagnostic and Statistical Manual of Mental Disorders definition and interviews (3).

The Pediatric Anesthesia Emergent Delirium (PAED) scale was the first validated delirium scale in children (15). Its use was limited to the detection of hyperactive delirium post anesthesia. In the PICU, the Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) was developed for use by nonpsychiatrists, as a modification of the adult Confusion Assessment Method for the ICU (3, 16). pCAM-ICU utility is limited by being validated in children over 5 years, with the majority of admissions comprising of children under 3 (6, 17). A number of additional tools have since been validated: the Cornell Assessment of PD (CAPD) for children of all ages (18) (a modification of the PAED) (15), the PreSchool Confusion Assessment Method for the ICU (psCAM-ICU) for children 6 months to 5 years old (a modification of pCAM-ICU) (19), the pCAM-ICU Severity Scale for children 5 years old or older (20), and the Sophia Observation Withdrawal Symptoms PD (SOS-PD) scale for children over 3 months old (21, 22). The European Society of Pediatric/Neonatal Intensive Care has recommended delirium assessment for all critically ill admissions (13).

Increased awareness and the development of validated tools have facilitated the reporting of PD prevalence, but estimates vary widely (11, 23). Differences in awareness, assessment tools, and geographical practice limit the generalizability of individual studies. Our hypothesis was that PD is common worldwide, and detection using validated bedside tools has potential for improving care. The aims were to calculate a pooled prevalence of PD, identify risk factors and management strategies, describe what is known about clinical outcomes, and highlight further areas for research.

MATERIALS AND METHODS

The primary review question was as follows: what is the prevalence of PD reported in critically ill children, estimated using validated scoring tools? Secondary questions included the following: what subtypes of delirium are observed, what scores are used, how is PD managed, what are the risk factors and clinical outcomes associated with PD—length of MV, ICU LOS, and mortality—and how does it impact admission costs? For the purposes of this review, and unless further differentiation is relevant, the term PICU is used to refer to PICU, neonatal ICU (NICU), and pediatric cardiac ICUs (PCICU). Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed (24, 25).

Randomized controlled trials (RCTs), cross-sectional, and cohort studies reporting the prevalence of PD in PICU using a validated tool were included. Nonresearch letters and editorials, seminar reviews, case studies, case series, case reports, abstracts, and animal studies were excluded. Studies describing delirium from other sources (alcohol, recreational drug use, postanesthesia emergent delirium) or non-ICU related were excluded. An information specialist assisted in developing the search strategy for PubMed, EMBASE, and CINAHL (**Supplemental Material**, http://links.lww.com/CCM/G836). Date and language restrictions were not applied. Citation and reference analysis was conducted. The final search was undertaken on October 18, 2020.

Citations were exported into EndNote Version 9 (Clarivate Analytics, London, United Kingdom), and duplicates eliminated. Two authors (D.S., J.C.H.) screened the titles and abstracts of all identified articles. Full text review of studies of uncertain eligibility

was performed (D.S., J.C.H.). A third author reviewed full texts where eligibility was uncertain. Data were extracted by an author (D.S.) and checked by one of the other coauthors for accuracy. Quality assessment was undertaken using the National Heart Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (26). Results from included studies were tabulated and described in a narrative synthesis. Heterogeneity of individual prevalence estimates was observed between PD assessment tools, and a minority of studies reported prevalence per assessment rather than prevalence per patient. As a result, a pooled prevalence estimate was restricted to the most commonly used tool (CAPD) and to studies reporting prevalence per patient. The pooled estimate and CI were calculated assuming a random effects model with inverse variance weighting; the method by DerSimonian and Laird (27) via the Metaprop command in STATA (Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX) (28).

RESULTS

Study Characteristics

Eight-hundred thirty-seven articles were identified. Removal of duplicates resulted in 671 articles for screening. Sixty met the inclusion criteria for full-text review. Thirty-seven articles were included in qualitative synthesis, with 31 containing prevalence data. Secondary analysis of studies that previously reported prevalence data was not included in prevalence extraction to avoid multiple counting of the same patients but was used to complement outcome data (29–34).

All included studies were published since 2011 (**Table 1**). All studies were observational in design, typically seeking to characterize PD or assess psychometric properties of the assessment tools. Twenty-seven (16, 18–22, 35, 38–43, 45–59) were prospective in design, two retrospective (36, 37), and two point prevalence (44, 58). Twenty-seven were single-center studies (16, 18–21, 36–43, 45–57, 59), and four were multicenter studies (22, 35, 44, 58), including two multisite point prevalence studies (44, 58). Twenty-seven took place in a PICU (16, 18–22, 35–43, 45–49, 52–54, 56–59), two in a PCICU (51, 55), one in a mixed PICU and PCICU (50), and one across multiple PCICUs or PICUs (44). No stand-alone NICU studies were found, but 18 included neonates (18, 36–38, 40–46, 50, 51, 53–56, 58). The 31 studies reported on 9,756 children. Twenty studies reported prevalence of PD using CAPD (18, 36–38, 40, 41, 43–46, 48, 50, 51, 53–59) or translated versions (40, 45, 46, 48, 53, 54), eight using variations of the pCAM-ICU (16, 19, 20, 35, 39, 47, 49, 52), and three the SOS-PD (21, 22, 42).

A quality assessment of 31 prevalence studies was undertaken (**Table 2**). Full-text English language articles were not available for three studies; therefore, quality assessment was not performed (45, 46, 48). Studies were generally of high quality. All studies clearly stated the research question, study population, and outcome measures.

Prevalence

Study information on the prevalence of PD is presented in **Supplementary Table 1** (http://links.lww.com/CCM/G668). Prevalence was reported per patient (n = 23) (19–22, 36–39, 41–46, 48–52, 56–59), per assessment (n = 4) (18, 40, 47, 53), or both (n = 4) (16, 35, 54, 55). Prevalence of PD using the CAPD tool ranged from 17% to 66% (18, 36–38, 40, 41, 43–46, 48, 50, 51, 53–59), 7% to 54% using age appropriate CAM-ICU (16, 19, 20, 35, 39, 47, 49, 52), and 10% to 25% using the SOS-PD (21, 22, 42). A pooled PD prevalence of 34% (95% CI, 27–41) was estimated from 17 studies that reported prevalence per patient using CAPD (**Fig. 1**) (36–38, 41, 43–46, 48, 50, 51, 54–59).

Eleven studies reported on the prevalence of PD subclasses (19, 22, 35, 36, 41, 43, 49, 51, 52, 57, 59). Of these, eight reported hypoactive PD as most prevalent (46–81%) (19, 35, 36, 43, 49, 51, 52, 57). Each of the three other studies reported either hyperactive (44%) (22), mixed (57%), or equal percentages of hypoactive and mixed delirium (43%) (59), as most prevalent.

Five studies reported on the time taken for PD to develop, with three reporting a majority of patients developing PD within 72 hours of PICU admission (22, 51, 55, 57, 58). Children diagnosed with delirium had twice the PICU LOS than those without (8 d [3–21 d] vs 4 d [2–14 d]; $p < 0.001$) (58). Prevalence of PD was reported as double for PICU stays exceeding 6 days (20% vs 38%) (58). Eight studies reported on the duration of delirium (19, 36, 37, 43, 46, 51, 54, 57). Those

TABLE 1.
Study Characteristics of Included Studies

References	Study Design	Location	Children Included, *n*	Age of Included Patients	PD Score Used	PD Definition
de Castro et al (35)	Prospective multisite cohort	Brazil	116	5–17 yr	pCAM-ICU (Brazilian-Portuguese version)	As per tool
Dechnik et al (36)	Retrospective single-site cohort	United States	734	0–21 yr	CAPD	≥ 9
Dervan et al (37)	Retrospective single-site cohort	United States	2,446	1 mo to ≥ 12 yr	CAPD	≥ 9
Gupta et al (38)	Prospective single-site cohort	United States	95	0–21 yr	CAPD	≥ 9
Henao Castaño and Pinzón Casas (39)	Prospective single-site cohort	Colombia	31	6 mo to < 6 yr	psCAM-ICU (Spanish version)	As per tool
Hoshino et al (40)	Prospective single-site cohort	Japan	41	0–13 yr	CAPD	≥ 9
Kaur et al (41)	Prospective single-site cohort	United States	40	0–21 yr	CAPD	≥ 9
Michel et al (42)	Prospective single-site before and after study	Germany	65	0–6 mo	SOS-PD	≥ 4
Silver et al (43)	Prospective single-site cohort	United States	207	0–5 yr	CAPD	≥ 9
Staveski et al (44)	Multisite point prevalence	United States and Canada	181	0–18 yr	CAPD	≥ 9
He et al (45)	Prospective single-site cohort	China	250	0–15 yr	CAPD	≥ 10
Hyo Jin and Dong Hee (46)	Prospective single-site cohort	South Korea	95	0–18 yr	CAPD	≥ 10
Matsuishi et al (47)	Prospective single-site cohort	Japan	19	6 mo to 5 yr	psCAM-ICU	As per tool
Navaeifar et al (48)	Prospective single-site cohort	Iran	72	Mean 3.88 ± 2.11 yr	CAPD	≥ 9
Ricardo Ramirez et al (49)	Prospective single-site cohort	Colombia	156	5–14 yr	pCAM-ICU (Spanish version)	As per tool
Valdivia and Carlin (50)	Prospective single-site cohort	United States	108	0–8 yr[a]	CAPD	≥ 9
Alvarez et al (51)	Prospective single-site cohort	United States	99	0–21 yr	CAPD	≥ 9
Cano Londoño et al (52)	Prospective single-site cohort	Colombia	77	5–14 yr	pCAM-ICU (Spanish version)	A s per tool
Ista et al (21)	Prospective single-site cohort	The Netherlands	146	3 mo to 16 yr	SOS-PD	≥ 4
Ista et al (22)	Prospective multisite cohort	The Netherlands	485	3 mo to 18 yr	SOS-PD	≥ 4

(*Continued*)

TABLE 1. (*Continued*)
Study Characteristics of Included Studies

References	Study Design	Location	Children Included, *n*	Age of Included Patients	PD Score Used	PD Definition
Simonsen et al (53)	Prospective single-site cohort	Denmark	30	0–16 yr	CAPD (Danish version)	≥ 8
Meyburg et al (54)	Prospective single-site cohort	Germany	93	0–17 yr	CAPD	≥ 9
Patel et al (55)	Prospective single-site cohort	United States	194	0–21 yr	CAPD	≥ 9
Simone et al (56)	Prospective single-site cohort	United States	821	0–24 yr	CAPD	≥ 9 for ≥ 48 hr
Traube et al (57)	Prospective single-site cohort	United States	1,547	0 to ≥ 13 yr	CAPD	≥ 9
Traube et al (58)	Multisite point prevalence	Multicontinent	994	0 to ≥ 13 yr	CAPD	≥ 9
Luetz et al (20)	Prospective single-site cohort	Germany	64	≥ 5 yr	pCAM-ICU Severity Scale, Pediatric Anesthesia Emergent Delirium	DSM-IV criteria
Smith et al (19)	Prospective single-site cohort	United States	281	6 mo to 5 yr	psCAM-ICU	Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria
Traube et al (18)	Prospective single-site cohort	United States	111	0–21 yr	CAPD	DSM-IV criteria
Silver et al (59)	Prospective single-site cohort	United States	50	3 mo to 21 yr	CAPD	DSM-IV criteria
Smith et al (16)	Prospective single-site cohort	United States	68	≥ 5 yr	pCAM-ICU	DSM-IV criteria

CAPD = Cornell Assessment of Pediatric Delirium, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, pCAM-ICU = Pediatric Confusion Assessment Method for the ICU, PD = pediatric delirium, psCAM-ICU = PreSchool Confusion Assessment Method for the ICU, SOS-PD = Sophia Observation Withdrawal Symptoms PD scale.
[a]Study open 0-23.8 yr but no participants > 8 yr old.

with a LOS over 48 hours and a diagnosis of PD had 2 extra PICU days compared with those without a diagnosis (37). A recurrence rate of 27% has been reported, with 5% of patients experiencing two or more distinct episodes of delirium (57).

Risk Factors and Associations

Risk factors were broadly classified as related to patient factors, clinical care, or pharmacotherapy interventions (Supplementary Table 1, http://links.lww.com/CCM/G668).

Patient Related

Twelve studies described associations between PD and age: nine younger ages (typically preverbal and under 2 yr) (18, 19, 37, 50, 51, 53–55, 57), and three older ages (22, 38, 46). Five studies identified developmental delay or baseline cognitive dysfunction as risk factors (18, 37, 49, 55, 57); PD was reported in 38% of children with developmental delay (41). Severity of illness was associated with higher PD scores ($n = 6$) (18, 37, 43, 51, 55, 57). Others reported risk factors related to primary

TABLE 2.
Quality Assessment of Included Studies ($n = 31$)

Study/Total Score	Q1 Objective Stated	Q2 Population Defined	Q3 Participation > 50%	Q4 Similar Populations	Q5 Power	Q7 Timeframe Sufficient	Q11 Outcome Measures Defined
de Castro et al (35)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Dechnik et al (36)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Dervan et al (37)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Gupta et al (38)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Henao Castaño and Pinzón Casas (39)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Hoshino et al (40)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kaur et al (41)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Michel et al (42)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Silver et al (43)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Staveski et al (44)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
He et al (45)/total NA							
Hyo Jin and Dong Hee (46)/total NA							
Matsuishi et al (47)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Navaeifar et al (48)/total NA							
Ricardo Ramirez et al (49)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Valdivia and Carlin (50)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Alvarez et al (51)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Cano Londoño et al (52)/total 5	Yes	Yes	Yes	Yes	No	Yes	No
Ista et al (21)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Ista et al (22)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Simonsen et al (53)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Meyburg et al (54)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Patel et al (55)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Simone et al (56)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Traube et al (57)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes

(*Continued*)

TABLE 2. (*Continued*)
Quality Assessment of Included Studies (*n* = 31)

Study/Total Score	Q1 Objective Stated	Q2 Population Defined	Q3 Participation > 50%	Q4 Similar Populations	Q5 Power	Q7 Timeframe Sufficient	Q11 Outcome Measures Defined
Traube et al (58)/total 5	Yes	Yes	Yes	Yes[a]	No	Yes	Yes
Luetz et al (20)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Smith et al (19)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Traube et al (18)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Silver et al (59)/total 6	Yes	Yes	Yes	Yes	No	Yes	Yes
Smith et al (16)/total 7	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NA = not applicable.
[a]Point prevalence that occurred in different days in different institutions but patient selection criteria remained the same.
Q1. Was the research question or objective in this article clearly stated? Q2. Was the study population clearly specified and defined? Q3. Was the participation rate of eligible persons at least 50%? Q4 Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? Q5. Was a sample size justification, power description, or variance and effect estimates provided? Q6. For the analyses in this article, were the exposure(s) of interest measured prior to the outcome(s) being measured? Q7. Was the timeframe sufficient, so that one could reasonably expect to see an association between exposure and outcome if it existed? Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure or exposure measured as continuous variable)? Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q10. Was the exposure(s) assessed more than once over time? Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q12. Were the outcome assessors blinded to the exposure status of participants? Q13. Was loss to follow-up after baseline 20% or less? Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? Q6, 8–10, and 12–14 deemed not suitable to this review and not accessed for any articles. Blank cells represent not accessed.

diagnosis, such as congenital cardiac malformations or cardiothoracic surgery (*n* = 4) (21, 44, 51, 55).

Clinical Care Related

Fourteen studies identified the need for respiratory support/MV as a risk factor for PD (18, 20, 22, 37, 38, 44–46, 49, 51, 55–58). Associations between development of PD and emergency admissions (20, 46) and cardiac disease (including cyanotic defects and postoperative state) (21, 51, 55) were also found. Other associations included the following: infections and inflammatory disorders (58), intellectual disability, neurologic and liver impairment (49), the use of physical restraints (37, 46, 55, 58), longer cardiac bypass times (51, 55), use of continuous renal replacement therapy (CRRT) (37, 44, 46), extracorporeal membrane oxygenation (44), and blood transfusions (31). A multisite point prevalence in postoperative cardiothoracic patients reported lack of documented ambulation, physical therapy, and parental presence during scoring as risk factors (44).

Pharmacotherapy Related

Benzodiazepine (21, 22, 29, 32, 37, 49, 51, 54, 55, 57, 58) and opioid (21, 22, 29, 37–39, 51, 55, 57, 58) use were commonly reported as PD risk factors (21, 22, 37–39, 51, 54, 55, 57, 58). For both, association between cumulative doses and PD was found (21, 29, 32, 37, 38). Other medicines identified as risk factors; anticholinergics (49, 51, 57), alpha$_2$-agonists clonidine (21) and dexmedetomidine (37, 55), vasoactive medications and inotropes (38, 55, 57, 58), ranitidine (19), omeprazole (19), furosemide (19), spironolactone (19), steroids (57, 58), and antiseizure medicines (58).

Management of PD

No study directly compared management strategies of PD. The introduction of a bundle that included regular

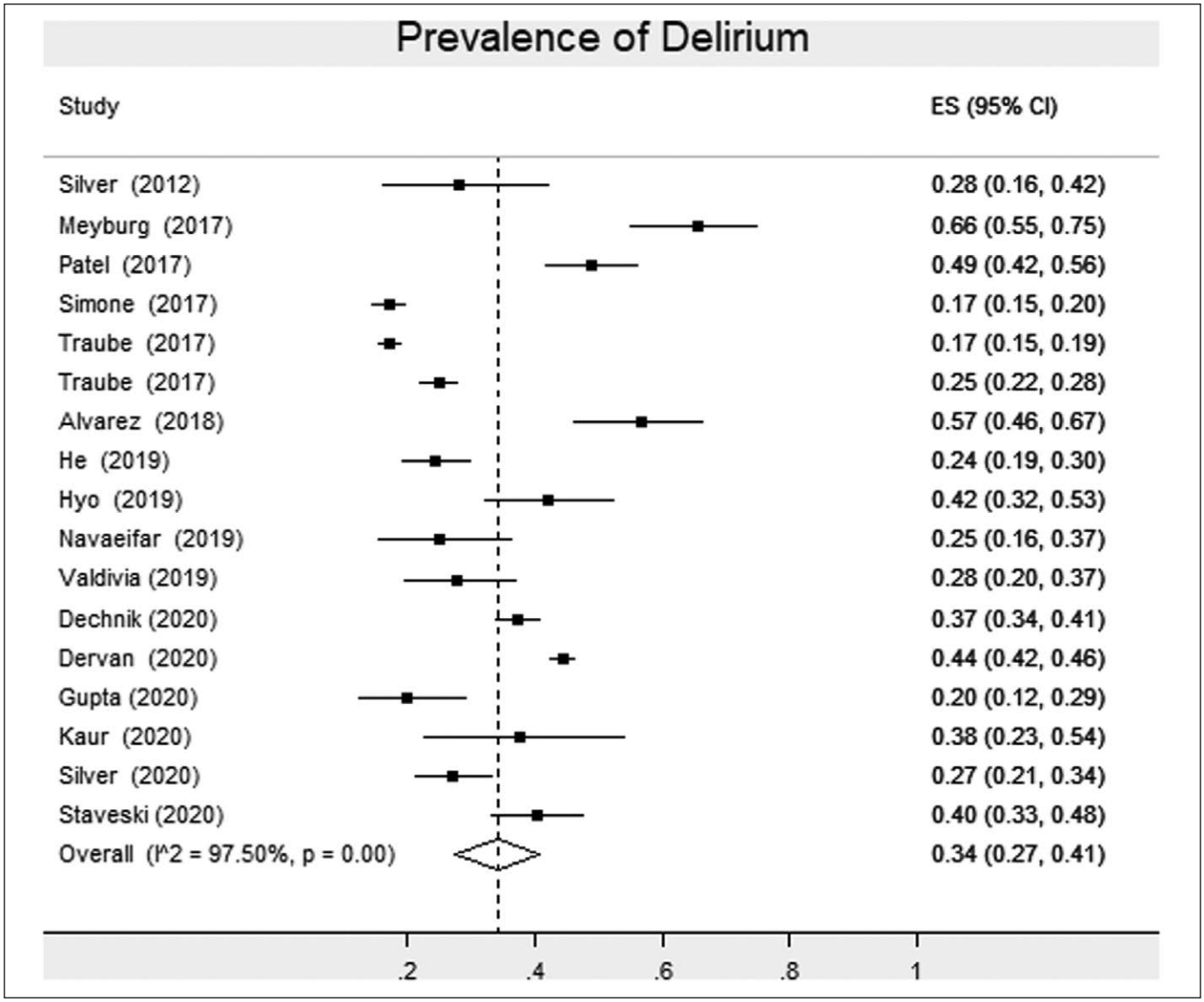

Figure 1. An estimate of pooled pediatric delirium prevalence per patient from studies ($n = 17$) using the Cornell Assessment of Pediatric Delirium assessment tool. ES = effect size.

pain/comfort assessment, sleep promotion, mobilization, and minimization of benzodiazepine use was associated with reduced PD rates (19% vs 12%) (56).

Association With Clinical Outcomes

Ventilation status and MV time are reported to be associated with a diagnosis of PD (20, 22, 37, 38, 44, 47, 49, 51, 55–58). Increases in MV time from 1.4 to four times were reported in patients with a diagnosis of PD (21, 37, 38, 44, 51, 55–57). Each day of PD is reported to increase LOS by 5% (37), with a two- to three-fold increase in LOS reported in patients with PD (20–22, 38, 39, 51, 54–58). PD is associated with higher in-hospital mortality (4.5% vs 0.7%; $p = 0.002$) and is reported as an early warning and stronger predictor of mortality than the Pediatric Index of Mortality 3 score (odds ratio, 4.4 vs 3.2) (20, 22, 36, 37, 57). Dervan et al (37) reported more days of PD in children who had died during a PICU stay (3 vs 2 d; $p < 0.0001$). However, when adjusted for severity of illness, days of coma, admission diagnosis, and CRRT, no independent association between PD and mortality for presence or days of delirium was found (37). PD has been associated with decreased quality of life after discharge from hospital and resolution of symptoms, even after controlling for severity of illness during hospitalization (43).

When adjusted for age, gender, severity of illness, and LOS, an 85% increase in costs, including an additional $14,000/PICU patient, was reported with PD (33).

DISCUSSION

We estimate a 34% (95% CI, 27–41%) prevalence of PD, with hypoactive delirium the most frequent phenotype, consistent with point prevalence reports from multiple continents. This suggests PD is a very frequent complication of critical illness in children regardless of geographical location and size (58). The particular population characteristics and treatment practices within institutions may influence the risk of developing PD. Examination of studies with high estimates suggests young children following cardiac surgery are at particular risk, with estimates of around one in two developing PD (44, 51, 54, 55). A range of additional risk factors may account for the apparent increased PD prevalence observed in PCICUs. These include the following: cardiopulmonary bypass time, systemic inflammatory response syndrome, nonpulsatile oxygen delivery, and thromboembolic events, all of which may lead to brain injury and inflammation (51). Conversely, studies with mixed populations or stricter definitions of PD classifications to exclude cross-over with emergence delirium reported lower estimates (21, 22, 56). Ista et al (21) suggest their lower prevalence of 9% may be due to increased PD awareness, leading to a culture that proactively minimizes the exposure to triggers.

Individual PD tool choice also accounts for some of the estimate variation. The SOS-PD is designed to be used for 48 hours after admission to exclude emergence delirium as a diagnosis. Studies using the CAPD from day 1 in postsurgical patients reported delirium often occurring on days 1–3 (37, 54, 55). Many of these children would have their delirium resolve before detection by other tools. In addition to this, psCAM-ICU is designed as an assessment of a specific time period, whereas CAPD and SOS-PD are based on an entire 12-hour nursing shift (16, 18, 19, 21). PD is a fluctuating and variable condition, and choice of tool may affect likelihood of detection. Additional factors such as younger age and presence of developmental delay make PD harder to diagnose. Detecting PD in younger nonverbal children is more difficult and dependant on experience (50). Those with developmental delay may be overrepresented in cardiac studies due to frequent comorbidities, leading to an overestimation of PD prevalence (44, 51, 55).

Identification and awareness of the dominant PD phenotype are important. Although hyperactive PD is more readily recognizable, hypoactive delirium is more common with children appearing docile and easy to care for and can be easily missed and associated with higher mortality (8, 51). Current practices for PD screening remain suboptimal; a cross-sectional study in 2014 identified almost three quarters of PICUs do not routinely screen for PD (10) with a 2020 study reporting less than half of included North American centers use a PD screening tool (44). Routine PD screening brings with it the potential for earlier diagnosis and intervention. At risk subgroups, such as children undergoing cardiac bypass surgery, have most to benefit (55).

Upon diagnosis, treatment approaches based on phenotype remain poorly differentiated. A number of case reports have proposed antipsychotics to manage PD, particularly the hyperactive presentation (57, 60–62). Whereas hypoactive delirium is less likely to respond to treatment with antipsychotics (57, 63–65). It may be possible to treat catatonia symptoms (stupor, negativism, stereotypy, minimal response to stimuli) of hypoactive delirium with benzodiazepines, ketamine, and antidepressants (7, 8, 66). Conversely, treatment of hyperactive delirium involves benzodiazepine exposure minimization (30). RCTs in children, cognizant of the different phenotypes and multifactorial causes of PD, are required to determine efficacy.

A lack of evidence to support treatment strategies for PD reinforces the need for prevention strategies. Nonpharmacologic approaches include those aimed at mitigating risk posed by disease processes, iatrogenic causes (IWS), and abnormal environmental factors (oversedation, pain, mobility) (57). Strategies to promote sleep hygiene, lighten sedation, and encourage early mobilization are all recommended and under investigation to reduce PD prevalence (10, 22, 67). Significant work to promote such interventions appears necessary as recent data suggest none are frequently implemented in North American units (44). Further research and evaluation of outcomes of quality improvement practices related to implementation of these protocols would be helpful.

The strengths of this review include the large number of patients, the overall quality of studies included, and the small number of validated assessment tools used. The dominance of the CAPD tool allowed estimation of a pooled prevalence within a cohort of studies. However, most studies were single sited,

retrospective, and observational in nature. This limits generalizability and determination of clinical order of exposures and outcomes along with causality of risk factors. This review has not determined conclusively the impact of delirium on mortality. Of the five articles reporting mortality outcomes, only two reported a difference in mortality, and a third reported a difference that was not significant after multivariable analysis. In addition, mortality breakdown for the different subtypes was not available. Mortality in PICUs is multifactorial, requiring carefully designed, longitudinal prospective studies to assess the impact of delirium on it. Other review limitations include the following: inconsistency in reporting outcomes, missing data, which may have led to an underestimate of PD prevalence, and overestimated prevalence from children with developmental delay. The pathophysiology of delirium, particularly in younger patients, and the effect of PD on long-term neurologic outcomes are poorly understood (57, 58). The costs (financial and nonfinancial) of caring for a delirious child merit further research (33, 68). A single U.S. study reported an 85% increase in PICU costs (nursing, laboratories, pharmacy, therapy, and radiology) associated with PD. Previous work in this area has estimated an increase of 1.5% for direct annual medical costs in a European PICU based on a conservative PD prevalence estimate of 5% (68). Differences in study methodology, medication costs, and/or advances in treatment may explain the differing estimates, and further study is required.

CONCLUSIONS

PD is prevalent in almost one third of PICU admissions and is an important contribution to length of MV, PICU LOS, mortality, and health service costs. Implementation of routine PD screening into all PICUs is overdue, with cardiac units having most to benefit due to higher prevalence in that subpopulation. Multicenter and longitudinal studies are required to identify modifiable risk factors, the natural history, true prevalence (including subtypes), long-term outcomes, and the financial implications of PD. Evidence-based pharmacologic and nonpharmacologic prevention and treatment strategies for delirium in critically ill children are required.

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