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CRITICAL REVIEW

Incidence and risk factors of posttraumatic epilepsy following pediatric traumatic brain injury: A systematic review and meta-analysis

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Abstract

Posttraumatic epilepsy (PTE) is a well-known chronic complication following traumatic brain injury (TBI). Despite some evidence that age at the time of injury may influence the likelihood of PTE, the incidence of PTE in pediatric populations remains unclear. We therefore conducted a systematic review to determine the overall reported incidence of PTE, and explore potential risk factors associated with PTE after pediatric TBI. A comprehensive literature search of the PubMed, Embase, and Web of Science databases was conducted, including randomized controlled trials and cohort studies assessing the incidence of PTE in TBI pediatric patients. We excluded studies with a sample size of <10 patients and those in which a pediatric cohort was not clearly discernable. The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We found that the overall incidence of PTE following pediatric TBI was 10% (95% confidence interval [CI] = 5.9%–15%). Subgroup analysis of a small number of studies demonstrated that the occurrence of early seizures (cumulative incidence ratio [CIR] = 7.28, 95% CI = 1.09–48.4, $p = .040$), severe TBI (CIR = 1.81, 95% CI = 1.23–2.67, $p < .001$), and intracranial hemorrhage (CIR = 1.60, 95% CI = 1.06–2.40, $p = .024$) increased the risk of PTE in this population. Other factors, including male sex and neurosurgical intervention, were nonsignificantly associated with a higher incidence of PTE. In conclusion, PTE is a significant chronic complication following childhood TBI, similar to in the adult population. Further standardized investigation into clinical risk factors and management guidelines is warranted. PROSPERO ID# CRD42021245802.

KEYWORDS

childhood, epilepsy, incidence, neurotrauma, pediatric, posttraumatic epilepsy, seizure, traumatic brain injury

1 | INTRODUCTION

Traumatic brain injury (TBI) affects 69 million individuals each year[1] and is associated with a number of chronic physical and cognitive complications, one of which is epilepsy.[2,3] Posttraumatic epilepsy (PTE) is a well-recognized long-term consequence of moderate and severe TBI in particular, and is defined as the occurrence of recurrent unprovoked seizures observed ≥7 days following the initial trauma.[4,5] The development of PTE is an added burden for affected individuals, being associated with increased neurological impairment, decreased cognitive function, and higher mortality.[6,7]

Although epilepsy after TBI in adult populations has been increasingly studied over the past decade, clinical understanding of the chronic consequences of TBI in pediatric cohorts remains understudied. The incidence of pediatric TBI hospitalization is reported to be 70 cases per 100 000 children,[8] and the risk of PTE, as well as prognostic implications of PTE in this population, has been poorly defined to date. Known and hypothesized differences in TBI mechanisms, biomechanics, and pathophysiology in pediatric TBI compared to adult TBI require that we consider the age at which injury is sustained as a key determinant of patient outcome. For example, abusive nonaccidental acceleration–deceleration injury is a mechanism unique to pediatric populations,[9] whereas developing neck muscles and a high head-to-body ratio results in a child's head being more vulnerable to sustaining a TBI.[10] The developmental stage of the brain at the time of injury also appears to play a role in the neuropathology of epileptogenesis,[11] including processes such as oxidative stress, neuroinflammation, and excitotoxicity.[11–13] Additionally, it has also been suggested that children have a higher risk of TBI following head injury.[11,14,15] As such, in the study of PTE as a clinically important outcome after TBI, it is vital to consider pediatric and adult cohorts as separate entities to aid in our understanding and guide appropriate clinical management.

A previous systematic review reported the incidence of PTE after TBI in adulthood to be approximately 15%, and a number of risk factors, including male sex, intracranial hemorrhage, and skull fracture, were identified.[16] However, in the current published literature, a consensus estimate of the incidence of PTE following TBI in pediatric patients is lacking, and the factors associated with PTE in children remain unclear. To address this knowledge gap, we conducted a systematic review to evaluate the incidence of PTE following childhood TBI. The primary aim of this study was to investigate the incidence of epilepsy diagnosis following pediatric TBI. Second, where the data were available, we aimed to identify risk factors for the development of PTE in pediatric populations.

Key Points

- The incidence of PTE following pediatric TBI is estimated to be approximately 10%.
- Early seizures, intracranial hemorrhage, and severe injury are statistically significant predictors of PTE.
- Standardization of future reporting will allow for improved comparability between studies.

2 | MATERIALS AND METHODS

2.1 | Protocol, registration, and ethics

The study was conducted as previously outlined in our registered and published protocol (PROSPERO ID# CRD42021245802)[17] and in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Table S1).[18] Considering the nature of the study (derived from previously published work), ethics approval and patient consent were not required.

2.2 | Search strategy

A comprehensive search of three electronic databases (PubMed, Ovid Embase, and Web of Science) was conducted in May 2021. Keywords included variations of the following: epilepsy ("epilepsy", "seizure", "status epilepticus"), traumatic brain injury ("traumatic brain injury" or "post-traumatic" or "traumatic" or "TBI" or "brain injury"), and pediatric ("pediatric" or "pediatric" or "newborn" or "infan*" or "child*"). Appropriate Boolean operators were used to combine search terms. The reference lists of all included studies were also reviewed to identify any additional articles, and duplicate articles were removed.

2.3 | Eligibility criteria

Our inclusion criteria allowed for randomized controlled trials and cohort studies that (1) reported TBI in patients younger than 18 years, (2) involved patients who developed PTE, and (3) included a sample size of 10 or more patients. Review publications, gray literature, conference abstracts, non-English language publications, and animal studies were excluded. Publications in which it was not possible to ascertain a specified study population of pediatric cases were excluded. Patients with an underlying

epileptogenic cause unrelated to the index TBI were also excluded.

Title and abstract screening was conducted by two independent investigators (F.P.M. and S.S.R.). Likewise, full-text screening was performed by two independent investigators (F.P.M. and P.S.). All conflicts were resolved by a third, senior investigator (B.D.S., T.J.O., or A.A.-B.). The systematic review platform Covidence (www.covidence.org; Veritas Health Innovation) was used to facility the screening process. Publications found to fulfill eligibility criteria underwent data extraction.

2.4 | Data extraction

Extracted variables included the number of TBI patients, number of PTE patients at follow-up, follow-up duration, patient demographics (age, sex, country), severity of injury, mechanism of injury (fall, motor vehicle accident, nonaccidental injury), occurrence of early seizures, skull fracture, intracranial hemorrhage, contusion, requirement of neurosurgical intervention, and use of antiseizure medications. All data extraction was performed by two independent investigators (F.P.M. and P.S.).

2.5 | Evaluation of risk of bias

Critical appraisal of the risk of bias for individual studies was conducted using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies.[19] Each included study was scored by two independent investigators (F.P.M. and P.S.). Any discrepancies between the two reviewers were resolved by discussion and mutual agreement. Publications that scored <5 points out of 11 were considered to be of poor quality, and were excluded from further analysis.

2.6 | Statistical analysis

A random-effects meta-analysis with DerSimonian and Laird method was used to calculate the pooled cumulative incidence of PTE after pediatric TBI. Heterogeneity was measured using the *I*-squared statistic (I^2), which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. Meta regressions were used to explore whether publication year or country of origin was the source of heterogeneity. *R*-squared (R^2) was calculated to quantify the heterogeneity that can be explained by the two variables. A funnel plot visual analysis and Egger test were applied to evaluate small study effect and publication bias for pooled PTE incidence in pediatric TBI. Freeman–Tukey double arcsine transformation was used on pooled PTE incidence in the funnel plot.

Where four or more studies were available, we performed subgroup meta-analysis to further investigate the effects of TBI subgroups (± a priori hypothesized potential risk factors) on the incidence of PTE, and calculated estimated cumulative incidence ratios (CIRs). Statistical significance level was set at $p < .05$. All statistical analyses were performed using Stata version 16 (StataCorp), with the user-written package "metaprop" for meta-analysis of proportions.[20]

3 | RESULTS

3.1 | Descriptive summary

Our electronic database search strategy of relevant references yielded a total of 2063 references (Figure 1). After removal of 532 duplicates, the remaining 1531 references were screened by title and abstract. A total of 114 publications were deemed to be eligible for full-text screening, of which 95 studies were excluded with reasons. A total of 19 articles were included in our final analysis, with a median sample size of 109 (range = 41–1576) and a pooled sample size of 4374 patients who sustained a pediatric TBI.[21–41] Ten publications were retrospective cohort studies, seven were prospective cohort studies, and two were randomized controlled trials. In 11 publications (58%), PTE was the primary outcome variable of interest, whereas PTE was investigated as a secondary outcome in the remaining eight publications. Seventeen studies exclusively analyzed pediatric cohorts, and the other two studies described mixed adult/pediatric cohorts from which the relevant study population could be extracted. Three publications were limited to severe TBI, one only investigated mild TBI, and one publication included moderate and severe TBI. The remaining 14 articles included all TBI patients regardless of severity. All publications defined pediatric patients as <18 years of age. Geographically, two publications were from the Middle East, four were from Asia, six were from North America, and seven were from Europe. A summary of the baseline characteristics of included papers and clinical variables is provided in Table 1.

3.2 | Incidence of PTE

Across the 19 included studies, the reported incidence of PTE in patients who had experienced pediatric PTE ranged from 1.9%[39] to 32%.[24] The pooled incidence of PTE, based on a random-effects model, was 10%

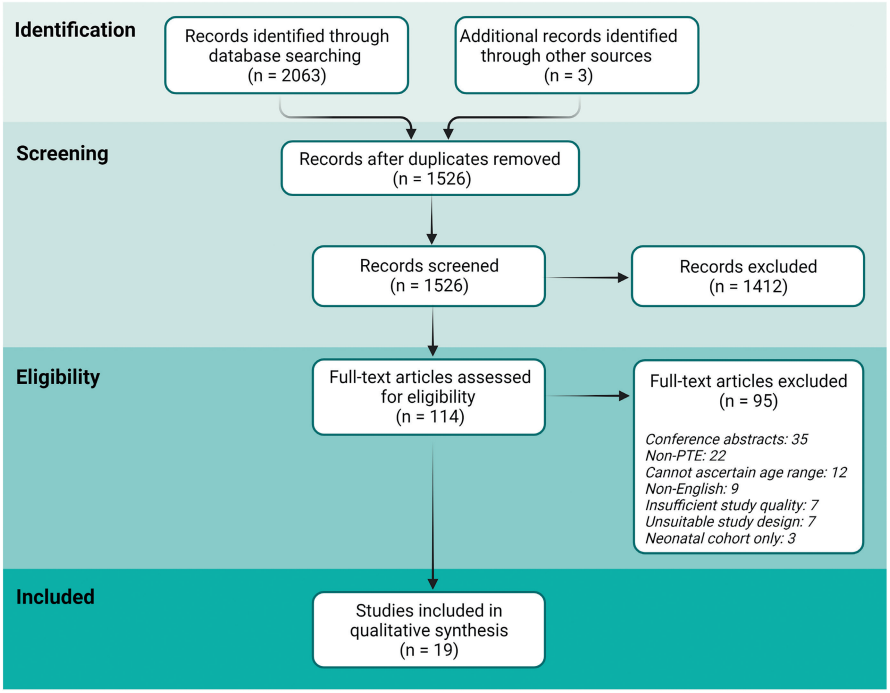

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of article screening. PTE, posttraumatic epilepsy.

(95% confidence interval [CI] = 5.9%–15%; Figure 2). There was high heterogeneity among the 19 studies (I^2 = 95%). Results of the meta-regression analysis demonstrated that country of origin could explain a substantial amount of heterogeneity (R^2 = 83%) but not year of publication (R^2 = 0%).

3.3 | Subgroup analyses to explore risk factors

To explore potential risk factors of PTE in pediatric populations, subgroup analysis was performed where sufficient information was available in four or more publications. Due to limitations in reporting in individual publications, we were unable to account for potential confounding variables; thus, analysis was univariate in nature.

The correlation between early seizures and PTE was assessed in four studies (Figure 3).[28,31,32,37] Patients with early seizures have 7.28 times the incidence of developing PTE of those without early seizures (95% CI = 1.09–48.4, p = .040). There is substantial between-study heterogeneity (I^2 = 73%). In addition, severe TBI (CIR = 1.81, 95% CI = 1.23–2.67, p < .001, I^2 = 0%; Figure 4) and intracranial hemorrhage (CIR = 1.60, 95% CI = 1.06–2.40, p = .024, I^2 = 0%; Figure 5) were also associated with elevated cumulative incidence of PTE, and the results of studies were relatively homogenous.

On the other hand, the cumulative incidences of PTE were not significantly different between females and males (CIR = .89, 95% CI = .46–1.71, p = .72, I^2 = 33%; Figure 6), and between patients requiring neurosurgical intervention and those not (CIR = 1.43, 95% CI = .91–2.26, p = .12, I^2 = 0; Figure 7).

Unfortunately, due to a lack of individual patient data, and between-study variation in the reporting of age ranges, it was not possible to perform subgroup analysis on the impact of age on PTE incidence.

3.4 | Study quality

Risk of bias was evaluated using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies (Table 2).[19] A total of 26 publications were eligible for quality assessment, of which seven publications were of low quality (score < 5/11) and excluded, and 19 publications were of sufficient quality to be included for further analysis (detailed above). The median score was 8 points out of a total of 11 (range = 5–11). The funnel plot examination did not demonstrate any apparent asymmetry (Figure 8), and Egger test (bias = 1.43, 95% CI = −2.13–4.99, p = .43) did not suggest presence of small study effect or publication bias. Of the included studies, the most common limitation in reporting was related to confounding variables and strategies of addressing incomplete follow-up. Only 11 publications (57.9%) identified and addressed confounding factors such as sex and other demographics in their analysis, and only seven publications (37%) specified strategies to address incomplete follow-up.

TABLE 1 Population characteristics

Author and date	TBI patients, *n*	PTE patients, *n*	Female, *n*	Severe TBI, *n*	Early seizures, *n*	Skull fracture, *n*	ICH, *n*	Contusion, *n*	Required neurosurgery, *n*
Appleton 2002	102	9	NR	NR	8	NR	NR	NR	NR
Arango 2012	130	22	44	130	NR	77	NR	NR	NR
Asikainen 1999	241	77	NR	NR	NR	NR	NR	NR	NR
Barlow 2000	42	8	NR	NR	NR	NR	NR	NR	NR
DeSantis 1979	52	8	NR	NR	2	NR	3	NR	NR
Emanuelson 2009	109	12	41	51	8	NR	NR	NR	17
Hwang 2019	68	7	26	NR	NR	30	NR	31	25
Kan 2006	51	10	18	51	NR	NR	NR	NR	51
Keret 2017	191	6	69	NR	6	139	58	29	9
Keret 2018	95	9	42	31	11	47	49	28	33
Matsumoto 2013	294	32	NR	27	NR	NR	NR	NR	NR
Mikkonen 2020	290	59	87	105	NR	NR	84	NR	57
Park 2015	321	47	NR	NR	NR	NR	NR	NR	NR
Pearl 2013	40	1	NR	NR	NR	NR	NR	NR	NR
Petridis 2012	238	15	106	15	26	25	NR	50	29
Ratan 1999	400	4	166	NR	84	NR	NR	NR	NR
Shin 2019	1576	30	621	8	NR	NR	NR	NR	NR
Thapa 2010	93	3	NR	NR	NR	NR	NR	NR	NR
Young 1983	41	4	NR	NR	NR	NR	NR	NR	NR

Abbreviations: ICH, intracranial hemorrhage; NR, not reported; PTE, posttraumatic epilepsy; TBI, traumatic brain injury.

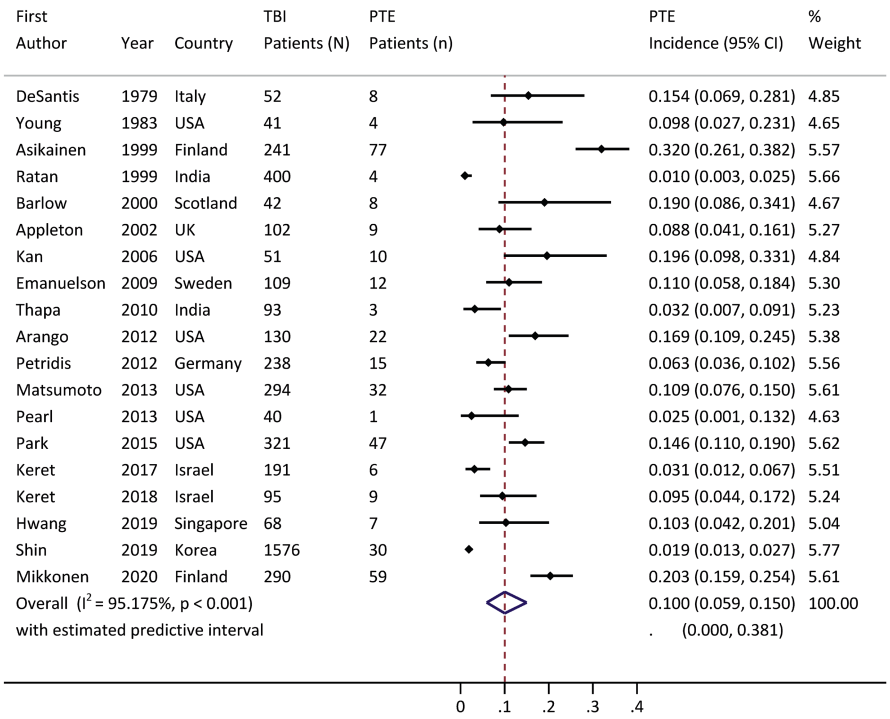

FIGURE 2 Pooled incidence of posttraumatic epilepsy (PTE) incidence, with 95% confidence interval (CI).

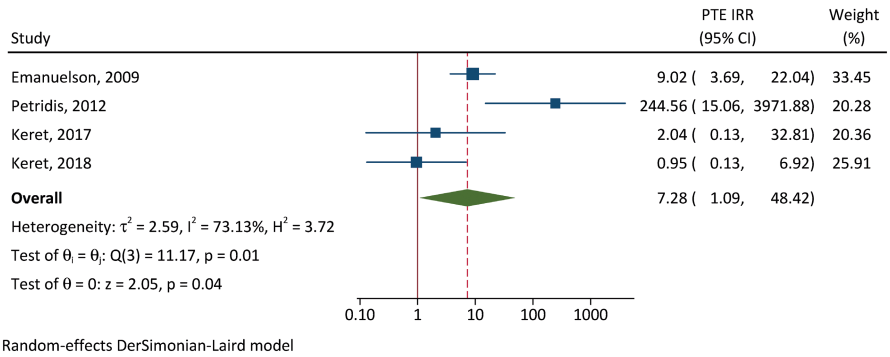

FIGURE 3 Correlation between early postinjury seizures and posttraumatic epilepsy (PTE). CI, confidence interval; IRR, incidence rate ratio.

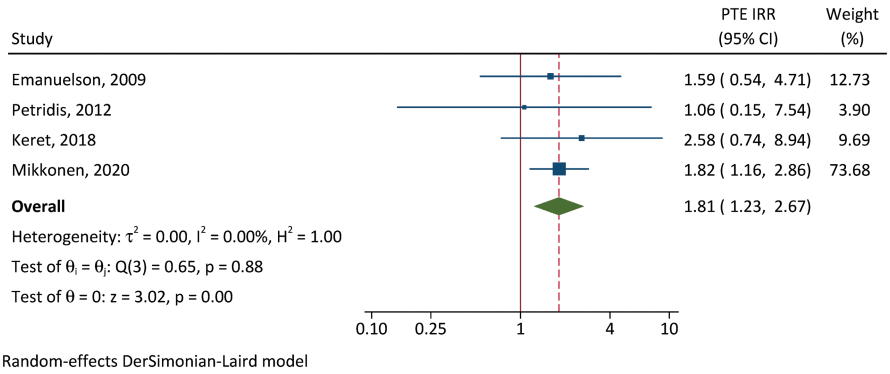

FIGURE 4 Correlation between traumatic brain injury severity and posttraumatic epilepsy (PTE). CI, confidence interval; IRR, incidence rate ratio.

4 | DISCUSSION

Our systematic review of the current literature found that the pooled incidence of PTE reported following childhood TBI is 10% (95% CI = 5.9%–15%), with quite a high level of heterogeneity in the 19 included publications (I^2 = 95%). Subgroup analyses revealed that early seizures (i.e., seizures within 7 days of sustaining a TBI), intracranial hemorrhage, and severe injury increase the risk of PTE. Other clinical variables, including male sex and requirement of neurosurgical intervention, tended to also be associated with a greater incidence of PTE, but did not

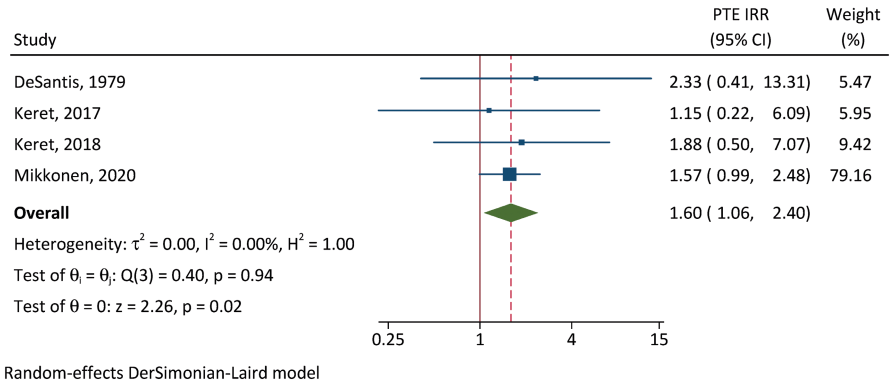

FIGURE 5 Correlation between intracranial hemorrhage and posttraumatic epilepsy (PTE). CI, confidence interval; IRR, incidence rate ratio.

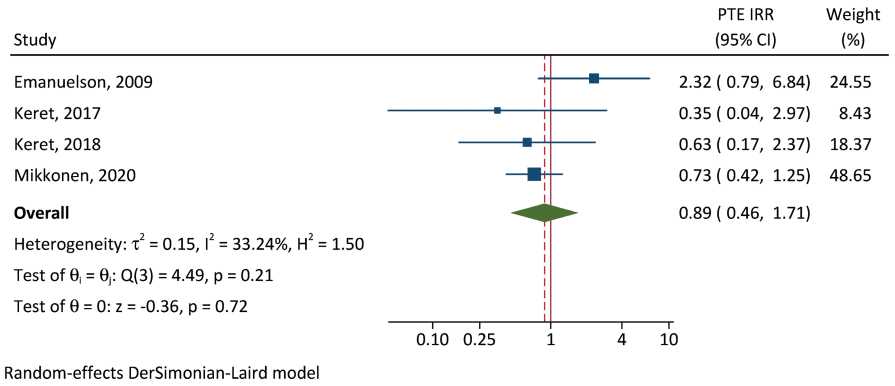

FIGURE 6 Correlation between female sex and posttraumatic epilepsy (PTE). CI, confidence interval; IRR, incidence rate ratio.

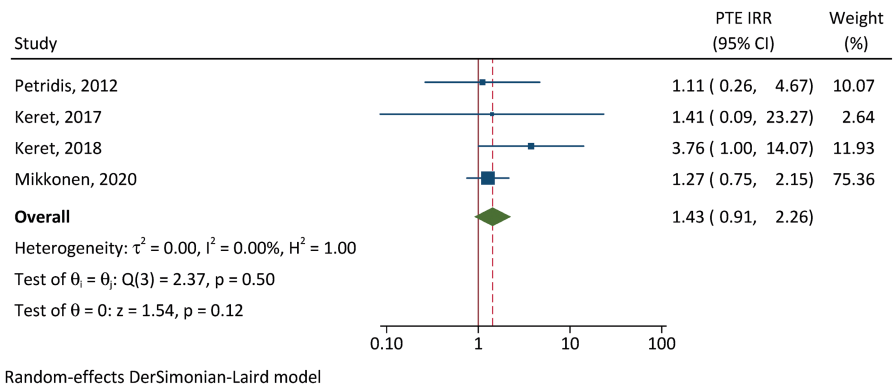

FIGURE 7 Correlation between neurosurgical intervention and posttraumatic epilepsy (PTE). CI, confidence interval; IRR, incidence rate ratio.

reach statistical significance, likely due to the low sample sizes.

Establishing the incidence of PTE following TBI in childhood is vital in understanding and highlighting the magnitude of TBI and its long-term complications. Sustaining a TBI during early life, particularly when the injury is severe, results in a substantial life-long burden to the individual, their families/carers, society, and the economy, not just in terms of health care resources but also in loss of earning potential across a lifespan.[42] PTE increases this burden, as the development of epilepsy post-TBI is associated with increased morbidity and mortality.[6,7] In adults, the risk factors and prevalence of PTE have been well described.[16] In pediatric cohorts, however, the clinical predictors of PTE are less clear, and a widely variable incidence has been reported by only a few studies. As secondary pathophysiological processes after TBI are increasingly understood to be dependent on the development age at the time of injury,[11,13] we now have a greater appreciation that findings from adult populations may not be directly applicable to a pediatric population.

This systematic review demonstrates that PTE is a significant outcome after TBI in childhood, with one in 10 children going on to develop epilepsy following TBI. A recent systematic review including adults found that PTE had a prevalence of 15%.[16] There may be several reasons for the increased incidence reported when compared to our review of pediatric cohorts alone. First, a very wide range has been reported for PTE incidence in adult studies, from 1% to 53%. Additionally, adult studies often include PTE

TABLE 2 Risk of bias evaluation

Author and date	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score
Appleton 2002	Y	Y	Y	Y	U	Y	Y	Y	U	U	Y	8
Arango 2012	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	8
Asikainen 1999	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	9
Barlow 2000	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	10
DeSantis 1979	Y	Y	Y	U	U	U	Y	Y	U	U	Y	5
Emanuelson 2009	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	10
Hwang 2019	Y	Y	Y	Y	Y	Y	Y	N	U	U	Y	8
Kan 2006	Y	Y	Y	Y	Y	U	U	N	Y	Y	Y	8
Keret 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Keret 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Matsumoto 2013	Y	Y	Y	U	U	Y	Y	U	U	U	Y	6
Mikkonen 2020	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	9
Park 2015	Y	Y	Y	Y	U	Y	Y	U	U	U	U	6
Pearl 2013	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	8
Petridis 2012	Y	Y	Y	U	U	Y	Y	U	U	U	Y	6
Ratan 1999	Y	Y	Y	U	U	Y	Y	U	U	U	Y	6
Shin 2019	Y	Y	U	Y	U	Y	Y	U	U	U	Y	6
Thapa 2010	Y	Y	Y	Y	Y	U	Y	N	U	U	Y	7
Young 1983	Y	Y	Y	Y	Y	U	Y	N	Y	Y	Y	9

Note: The Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies,[19] as used, incorporated the following series of questions. Q1: Were subjects recruited from the same population? Q2: Was TBI measured comparatively? Q3: Was TBI measured in a valid and reliable way? Q4: Were confounding variables identified? Q5: Were strategies to deal with confounding factors stated? Q6: Were subjects free from epilepsy at the start of the study / at exposure to TBI? Q7: Was epilepsy measured in a valid and reliable way? Q8: Was the follow-up time reported and sufficient to be long enough for epilepsy to occur? Q9: Was follow-up complete, and if not, were the reasons described/explored? Q10: Were strategies to address incomplete follow-up utilized? Q11: Was appropriate statistical analysis used?

Abbreviations: N, no; TBI, traumatic brain injury; U, unknown; Y, yes.

FIGURE 8 Funnel plot analysis. The apparent asymmetry suggests a lack of publication bias. PTE, posttraumatic epilepsy.

in military veterans, which may add a layer of complexity due to different injury mechanisms and comorbidities in this population. In our review, the vast majority of studies included mild TBI cases, which may have impacted the overall incidence. For instance, Shin et al.[39] reported an incidence of 3.4% in 1576 patients, with 99% of patients only experiencing mild TBI. Finally, our study investigated all patients younger than 18 years, which encompasses a wide range of distinct neurodevelopmental periods. It has been suggested that developmental windows during infancy and early childhood may be particularly susceptible to seizures and epilepsy.[43,44] Due to limitations in reporting by the included studies, we were unable to stratify according to age, which may have provided a more accurate representation of epilepsy vulnerability in children of different developmental stages. We recommend that future studies pay close attention to age at the time of injury as a potential variable that may influence the incidence of PTE.

In this study, we determined that early seizures increased the risk of PTE, and analysis also demonstrated that severe TBI was strongly associated with PTE. Ultimately, inconsistencies in the definitions and classification of TBI severity prevented the inclusion of more studies in this subgroup analysis. Future studies would be well served by a standardization of definitions (e.g., Glasgow Coma Scale) and reporting to ensure comparability.

Our findings add to the growing body of evidence emphasizing the long-term ramifications of childhood TBI and highlighting the vital need for public education regarding TBI in children. In particular, the incidence of abusive head trauma may be increasing, according to recent reports,[45,46] and the implementation of preventive measures may improve awareness and increase the identification of red flags and warning signs.[47,48] Additionally, motor vehicle accidents are a significant source of head injury in children, and parental education concerning motor vehicle safety in children may play a key role in reducing the risk of head injury secondary to road accidents.[49]

This study has a number of strengths. It is relatively representative of the worldwide incidence of PTE following pediatric TBI, with studies sourced from more than 12 countries across Asia, Europe, North America, and the Middle East. Our systematic review also incorporated a relatively large total sample size of almost 5000 patients from 19 studies. Our eligibility criteria were stringently enforced, ensuring that publications were of sound quality, with a particular emphasis on including pediatric patients only, and excluding cohorts where age was unclear.

However, we also note several limitations to the analysis. There was significant heterogeneity in the clinical variables reported by different publications, with very limited reporting of relevant variables, including clinical, radiological, and treatment characteristics. Consequently, despite a relatively large sample size, very few studies reported sufficient detail to be included for further subgroup analyses. As such, we were unable to thoroughly investigate predisposing factors and clinical variables that may increase the risk of PTE. Furthermore, many survivors of TBI report new onset neuropsychiatric conditions and neurocognitive deficits—comorbidities that are also common in individuals with epilepsy.[50] Nonetheless, the potential for such comorbidities to influence PTE incidence, in either adult or pediatric populations, remains poorly explored. Another limitation to note was that our search strategy and article selection excluded non-English publications, which may have provided more data. Finally, most studies included in this review were retrospective in nature, which introduces several forms of bias into the literature, limiting the strength of conclusions drawn.

Regardless, our findings highlight that future investigation into childhood TBI and its ramifications is clearly warranted, and provides direction for improving future research in the field. Despite increasing awareness and interest in pediatric TBI and epilepsy, this review identifies a strong need for further and more rigorous examination. Large, prospective studies with a focus on identifying population subgroups at increased risk of developing PTE would provide significant insight. Additional variables such as patient demographics, clinical presentation, severity of injury, and radiological findings may also provide prognostic value. Additionally, investigation into injury mechanisms would have widespread implications, with specific consideration of nonaccidental injury and its long-term impacts on children. Furthermore, study into the clinical management of TBI and its impact on developing PTE may propel investigation into treatments and strategies to reduce the risk of PTE. Finally, future studies should adopt more standardized reporting of results and utilization of consensus-agreed clinical definitions to allow for better comparability between studies, allowing for a more uniform body of evidence from which robust conclusions can be drawn.

5 | CONCLUSIONS

In the reported literature, the overall incidence of PTE following pediatric TBI is 10.0%. Seizures within 1 week of initial presentation, intracranial hemorrhage, and severe injury were significantly associated with an increased risk of PTE, and other factors such as male sex and neurosurgical intervention showed a greater risk that was not statistically significant. This review ultimately highlights the vital need for further investigation into childhood TBI and its complications, with a focus on standardized reporting of clinical findings.

AUTHOR CONTRIBUTIONS

Frederick P. Mariajoseph, Terence J. O'Brien, Ana Antonic-Baker, and Bridgette D. Semple conceived and designed the project. Frederick P. Mariajoseph, Praba Sekhar, and Sarah S. Rewell conducted the systematic review with guidance from Bridgette D. Semple and Ana Antonic-Baker. Zhibin Chen performed the statistical analyses, and Terence J. O'Brien provided critical input in planning the study protocol. Frederick P. Mariajoseph, Ana Antonic-Baker, and Bridgette D. Semple drafted the manuscript. All authors read, edited, and approved the final manuscript prior to submission.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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