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RESEARCH ARTICLE

Association between pediatric traumatic brain injury and epilepsy at later ages in Finland: A nationwide register-based cohort study

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Abstract

Objective: This study was undertaken to examine how pediatric traumatic brain injury (pTBI) correlates with incidence of epilepsy at later ages in Finland.

Methods: This nationwide retrospective register-based cohort study extended from 1998 to 2018. The study group consisted of 71 969 pediatric (<18 years old) patients hospitalized with TBI and a control group consisting of 64 856 pediatric patients with distal extremity fracture. Epilepsy diagnoses were gathered from the Finnish Social Insurance Institution. Kaplan–Meier and multivariable Cox regression models were conducted to analyze the probability of epilepsy with 95% confidence intervals (CIs).

Results: Cumulative incidence rates (CIRs) for the first 2 years were .5% in the pTBI group and .1% in the control group. The corresponding rates after 15 years of follow-up were 1.5% in the pTBI group and .7% in the control group. Due to proportional hazard violations, the study population was split to the first 2 years and in subgroup analysis 4 years. During the first 2 years of surveillance, the hazard ratio (HR) for the pTBI group was 4.38 (95% CI = 3.39–5.66). However, between years 2 and 20, the HR for the pTBI group was 2.02 (95% CI = 1.71–2.38). A total of 337 patients (.47%) underwent neurosurgery, and 36 (10.7%) patients subsequently developed epilepsy. The CIR for the first year after TBI was 4.5% (95% CI = 2.3–6.7) in operatively managed patients and .3% (95% CI = .3–.4) in nonoperatively managed patients. Corresponding figures after 15 years were 12.0% (95% CI = 8.2–15.8) and 1.5% (95% CI = 1.4–1.6). During the first 4 years of surveillance, the HR for the operative pTBI group was 14.37 (95% CI = 9.29–20.80) and 3.67 (95% CI = 1.63–8.22) between years 4 and 20.

Significance: pTBI exposes patients to a higher risk for posttraumatic epilepsy for many years after initial trauma. Children who undergo operative management for TBI have a high risk for epilepsy, and this risk was highest during the first 4 years after injury.

KEYWORDS
epilepsy, pediatric, posttraumatic epilepsy, PTE, TBI, traumatic brain injury

1 | INTRODUCTION

Traumatic brain injury (TBI) is defined as an alteration of brain function or brain pathology due to an external force.[1–3] TBI is also associated with several neurodegenerative diseases in adults, such as early Alzheimer disease and Parkinson disease. However, long-term neurological morbidity after pediatric TBI (pTBI) is still an understudied subject.[4,5]

The incidence of TBI in the pediatric and young adolescent populations in Finland has been studied extensively. However, prior studies have not depicted posttraumatic complications, effects on quality of life, or neurological problems experienced after TBI.[6,7] A large Finnish cohort study of 72 000 patients with pTBI who were hospitalized between 1998 and 2018 demonstrated that the annual incidence of pTBI increased by 118% during the 20-year study period, increasing from 251 per 100 000 in 1998 to 547 per 100 000 in 2018.[8]

Various studies indicate that TBI may be a risk factor for later onset epilepsy.[9,10] TBI can cause posttraumatic seizures that usually appear seconds to hours after an injury is sustained and can contribute to the development of posttraumatic epilepsy (PTE). Early onset seizures (<7 days after TBI) are, however, a relatively rare complication after TBI, with a prevalence ranging from .4% to 4.5%.[11–14] In contrast, pTBI is associated with early onset seizures. In a study cohort of 87 patients, 43.7% had seizures and the risk was higher at a younger age.[15] A large Danish cohort study that included more than 1.6 million children and young adults reported an increased risk for epilepsy after mild TBI. The reported risk ratio for mild TBI was 2.22, for severe TBI 7.40, and for skull fracture 2.17. Furthermore, the risk remained for more than 10 years after sustaining the injury.[16] A meta-analysis of 19 articles on pTBI-related PTE with a pooled sample size of 4374 patients had an incidence of PTE of 10%. There was, however, no significant difference in cumulative incidence ratio (CIR) between those patients who needed neurosurgical intervention and those who received nonoperative management (CIR = 1.43).[5]

Although a few large cohort studies have investigated the prevalence of epilepsy caused by pTBI, the association between operatively managed pTBI and later onset epilepsy has not been widely studied. Therefore, we aim to examine how pTBI correlates with the incidence of epilepsy at later ages in the Finnish population, and how the rate of TBI (operatively managed TBI and nonoperatively managed TBI) cumulates in a diagnosis of epilepsy.

Key Points

- Pediatric TBI is associated with higher risk for PTE for many years after sustaining initial trauma
- Children who undergo operative management for TBI have a higher risk for epilepsy
- The risk for epilepsy was highest during the first 4 years after sustaining pediatric TBI requiring operative management
- Surveillance bias is a possible limitation, as increasing awareness and clinical classification of TBI in both adult and pediatric populations during the follow-up period have led to increased rates of TBI

2 | MATERIALS AND METHODS

Data for this nationwide retrospective register-based cohort study were collected from two national registers: the Finnish Care Register for Health Care and the Finnish Social Insurance Institution. The study period was from January 1998 to December 2018.

The primary study group consisted of all pediatric patients, both inpatients and outpatients (aged younger than 18 years) with TBI (International Classification of Diseases, 10th Revision [ICD-10] codes S06*). This group underwent either operative or nonoperative management in a specialized health care unit. Data were collected from the Finnish Care Register for Health Care, which is maintained by the Finnish Institute of Health and Welfare (THL). The register contains patient information for all secondary and tertiary level specialized health care visits, operations, and hospitalizations in Finland. The rate of TBI-related neurosurgical operations was based on the NOMESCO Classification of Surgical Procedures codes (Finnish version). The total number of operations was calculated using the operation codes. Thus, those patients who had multiple operations during one hospitalization were separated using their unique identification codes and the dates of primary injury to evaluate the number of cases. The codes did not contain intracranial pressure

(ICP) probe installations because of the unreliability of a number of ICP probe installation recordings in the Finnish Care Register for Health Care.

The control group consisted of all pediatric patients aged between 0 and 17 years who had sustained an ankle (ICD-10 S82.5 and S82.6) or wrist fracture (ICD-10 S62.5 and S62.6) requiring hospital treatment between January 1998 and December 2018. The patients with fractures in the control group were selected for the study because their behavioral profile, including hobbies and sports, was deemed similar to that of children with TBI, and therefore the risk for physical injury between groups was also similar.

The collected data included the day of hospitalization due to TBI or fracture, age at the time of injury, and gender. Patients who were diagnosed with epilepsy prior to sustaining TBI or fracture and those patients who had only one seizure were excluded. If a patient had both TBI and distal extremity fracture, they were included in the TBI group.

TBI was divided into two groups in subgroup analysis: nonoperatively managed and operatively managed.

The total number and onset of epilepsy diagnoses were coded using the special reimbursement codes 111 and 182 for epilepsy from the Finnish Social Insurance Institution. To obtain these codes, a comprehensive neurological assessment by a specialized health care provider is necessary. Diagnosis of epilepsy is confirmed by a pediatric neurologist, and this classification encompasses all the antiseizure medications prescribed for epilepsy treatment in Finland. As all pediatric patients with epilepsy in Finland receive a reimbursement for epilepsy treatment expenses, our study included all Finnish pediatric patients diagnosed with epilepsy. However, only diagnoses of post-injury epilepsy were considered as injury-related and used in the analysis.

2.1 | Statistical analysis

Descriptive statistics were presented as *n* (%) and as median with interquartile range based on the distribution. If a patient had more than one hospitalization due to the injury, only the first was used in the analysis. Kaplan–Meier (KM) survival analysis was used to analyze the probability of epilepsy with 95% confidence intervals (CIs) between the pTBI group and the control group from the day of the hospitalization to the diagnosis of epilepsy. Results were reported as cumulative incidence rates.

Multivariable Cox proportional hazard regression analysis was used to compare epilepsy-free survival between study groups after adjusting confounding variables. The results of Cox regression were interpreted with hazard ratios (HRs). Epilepsy was used as the dependent variable, and all analyses were adjusted for potential confounders, which included age at the moment of hospitalization and gender. Violations of proportional hazard (PH) assumptions were examined by evaluating the correlation of scaled Schoenfeld residuals with time.

Furthermore, the correlation of scaled Schoenfeld residuals and log–log survival curves were inspected visually to evaluate the PH assumptions. A time stratified model[17] was constructed to handle PH assumption violations. Correlations of Schoenfeld residuals with time were repeatedly evaluated to ensure that nonproportionality was fixed. To fix the nonproportionality, a time-dependent coefficients method was used to split the study population between 0 and 2 years of surveillance and between 2 and 20 years of surveillance.

Subgroup survival analyses were performed to analyze the epilepsy-free survival differences between operatively managed pTBI and nonoperatively managed pTBI. The KM survival analysis and multivariable Cox proportional hazard regression analysis were used as in the main analysis. Epilepsy was used as the primary dependent variable, and all analyses were adjusted for potential confounders, which were age at the moment of hospitalization, gender, and operative management. PH violations were evaluated and handled as in the main analysis, and time-dependent coefficient technique was used to split the study population between 0 and 4 years of surveillance and between 4 and 20 years of surveillance.

All analyses and figures were performed using Windows R version 4.0.5 (2021-03-31; R Foundation for Statistical Computing) with the packages tidyverse, ggfortify, survival, and survminer.

2.2 | Ethics

Due to the retrospective nature of this cohort study, no ethical committee approval was needed. All collected data were pseudonymized according to the Personal Data Act 10§. Pseudonymization was performed by Statistics Finland, and none of the authors had access to the data. The data were handled in a safe remote-controlled environment that required two-phase identification at every login. The Finnish data authority, Findata, gave permission to access the Care Register (permission number THL/4397/14.06.00/2022). Statistics Finland gave permission to access the Population Information and Register of Death Causes (permission number TK/110/09.01.01/2020). According to Finnish law on the secondary use of patient information, our data cannot be made freely available. Furthermore, researchers living outside Finland are prohibited from accessing Finnish

register data. This study follows the ethical guidelines of the Declaration of Helsinki.

3 | RESULTS

The data of 137 794 patients were collected from the Finnish Care Register for Health Care and the Finnish Social Insurance Institution. After 969 exclusions due to insufficient medical data or diagnoses, a total of 136 825 patients were included in this study (Figure 1). The primary study group consisted of 71 969 patients with TBI and 64 856 controls. Altogether, 4012 patients had both a TBI and a fracture (Table 1).

A total of 2047 patients had epilepsy at the end of the study period. Of these, 962 had an epilepsy diagnosis before TBI or ankle/wrist fracture and 1085 developed epilepsy after sustaining the injury. Of these, 784 (1.10%) were in the TBI group and 301 (.46%) in the control group. Median age at time of hospitalization was 7 years in the TBI group and 11 years in the control group. In the pTBI group 58% of patients were male, and in the control group 62% were male (Table 2).

During the first 2 years of surveillance, cumulative incidence rates for epilepsy were .5% (95% CI =.5–.6) in the TBI group and .1% (95% CI = .1–.1) in the control group. The cumulative rate 15 years after the study started was 1.5% (95% CI = 1.4–1.6) in the TBI group and .7% (95% CI = .6–.7) in the control group (Table 3, Figure 2). In comparison, a previous Norwegian study suggests that the prevalence of childhood epilepsy ranges between .5% and 1%. Furthermore, the incidence of Finnish pediatric epilepsy was 76.5/100 000 in boys and 66.8/100 000 in girls in 2002.[18,19]

Based on Cox regression, patients with pTBI had a higher risk for epilepsy compared to the control group. After the first 2 years of follow-up, the HR for the TBI group was 4.38 (95% CI = 3.39–5.66) and 2.02 (95% CI = 1.71–2.38) between years 2 and 20.

In total, 337 patients (.47%) underwent operative management for TBI. Of these, 36 patients (10.7%) developed epilepsy later. Cumulative incidence rates for the first year after TBI were 4.5% (95% CI = 2.3–6.7) in operatively managed patients and .3% (95% CI = .3–.4) in nonoperatively managed patients. However, the corresponding figures after 15 years of surveillance were 12.0%

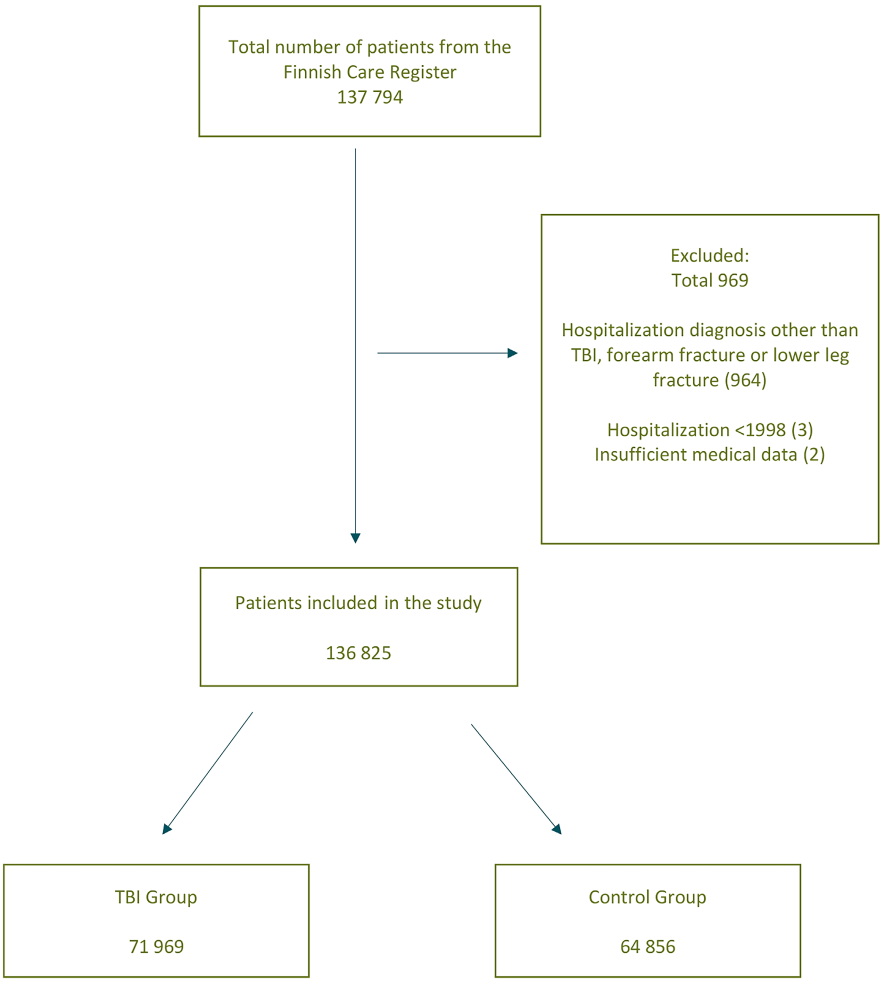

FIGURE 1 Flowchart of inclusion and exclusion of the study population. TBI, traumatic brain injury.

(95% CI = 8.2–15.8) and 1.5% (95% CI = 1.4–1.6; Table 4, Figure 3).

Patients who had operatively managed TBI had a higher risk for developing epilepsy than patients who had nonoperatively managed TBI. During the first 4 years of surveillance, HR was 14.37 (95% CI = 9.29–20.80). However, between years 4 and 20, HR was 3.67 (95% CI = 1.63–8.22).

4 | DISCUSSION

The findings of our study demonstrate that patients with pTBI have an increased risk for PTE compared to a control group of distal extremity fracture patients. The risk for epilepsy is 4.4 times higher for the first 2 years after sustaining TBI and approximately 2 times higher 20 years after injury. Moreover, the risk for developing epilepsy is higher in those patients who have operatively managed TBI. PTE risk is 14 times higher during the first 4 years after operatively managed injury and 3.7 times higher 20 years after injury.

The literature on pTBI-related epilepsy is sparse. Compared to the few other previously published studies, our findings concerning nonoperatively managed TBI are similar to those of a large Danish cohort study.[16] However, our results suggest that operatively managed TBI, which could imply more severe TBI, had a much higher risk for developing epilepsy at a later age. The Danish study reported a risk ratio of 7.40 for severe TBI-related epilepsy. Furthermore, a small Israeli cohort study found the risk for severe TBI-related epilepsy was 2.9 times higher, whereas in our study HR for operatively managed TBI was 14.4 times higher than for nonoperatively managed TBI.[20] A smaller cohort study of 321 children found that 83% of patients with severe TBI had PTE.[21]

Our results correlated with a meta-analysis of 19 studies on pTBI-related PTE. The authors of the meta-analysis reported a pooled incidence of PTE of 10% and found a correlation with severe TBI (CIR = 1.81) and PTE. However, the cumulative incidence ratio for operatively managed patients with pTBI was only 1.43. In contrast, our results indicated a much higher correlation between PTE and the operative management of pTBI. However, the difference between studies concerning operatively managed TBI can stem from national differences in medical systems and variations in access to surgical operations. The

TABLE 1 Inclusion and exclusion criteria of the study population.

Inclusion criteria	Exclusion criteria
Age < 18 years	Insufficient medical data
Treated 1998–2018	
TBI or distal extremity fracture	
Treated in special health care unit	

Abbreviation: TBI, traumatic brain injury.

TABLE 2 Gender, median hospitalization year, and age distribution in pTBI-related epilepsy in Finland from 1998 to 2018.

	TBI group	Control group	Operative TBI group	Nonoperative TBI group
Patients, *n*	71 969	64 856	337	71 632
Median age at the time of trauma, years	7 (3–13)	11 (8–14)	12 (6–16)	7 (3–13)
Gender, *n* (%)				
Male	41 496 (58%)	40 111 (62%)	243 (72%)	41 253 (58%)
Female	30 473 (42%)	24 745 (38%)	94 (28%)	30 379 (42%)
Epilepsy, *n* (%)	784 (1.10%)	301 (.46%)	36 (10.70%)	748 (1.04%)
Median hospitalization year	2011 (2004–2015)	2008 (2003–2014)	2008 (2003–2013)	2011 (2004–2015)

Abbreviations: pTBI, pediatric TBI; TBI, traumatic brain injury.

TABLE 3 Kaplan–Meier table of cumulative incidence of epilepsy at 1–15 years after pediatric trauma in TBI and distal extremity fracture groups in a Finnish nationwide sample.

		At 1 year		At 2 years		At 10 years		At 15 years	
	N.of	*n*.risk	Cumulative incidence (CI)	*n*.risk	Cumulative incidence (CI)	*n*.risk	Cumulative incidence (CI)	*n*.risk	Cumulative incidence (CI)
TBI	71 696	66 605	.3%(.3–.4)	61 022	.5%(.5–.6)	29 948	1.2%(1.1–1.3)	16 786	1.5%(1.4–1.6)
Control	64 856	61 439	.1%(.–.1)	58 137	.1%(.1–.1)	33 803	.5%(.4–.5)	19 412	.7%(.6–.7)

Abbreviations: CI, confidence interval; *N*.of, number of patients; *n*.risk, number at risk; TBI, traumatic brain injury.

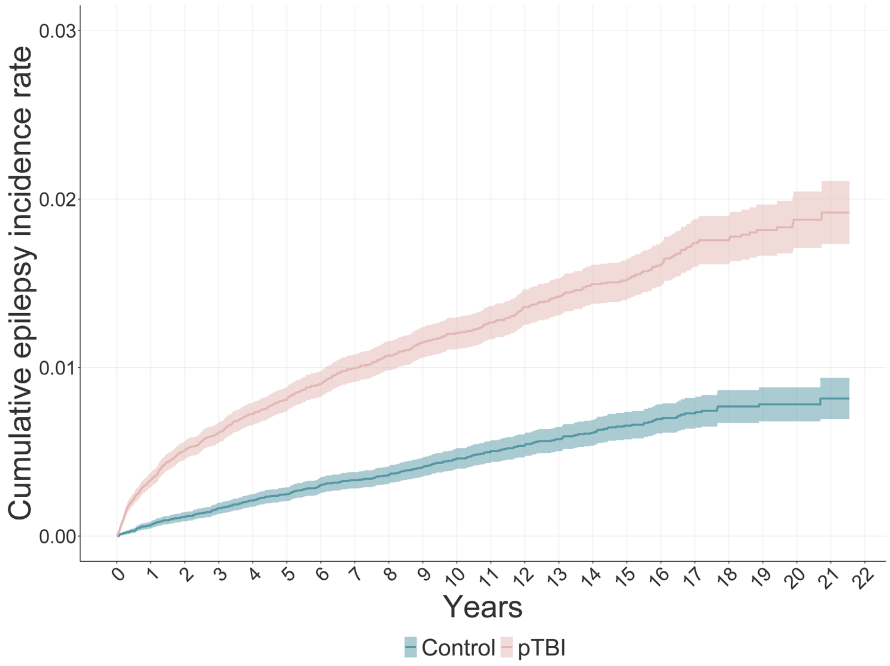

FIGURE 2 Kaplan–Meier curve of the cumulative epilepsy incidence rate in the study population with 95% confidence intervals for pediatric traumatic brain injury (pTBI) in Finland from 1998 to 2018.

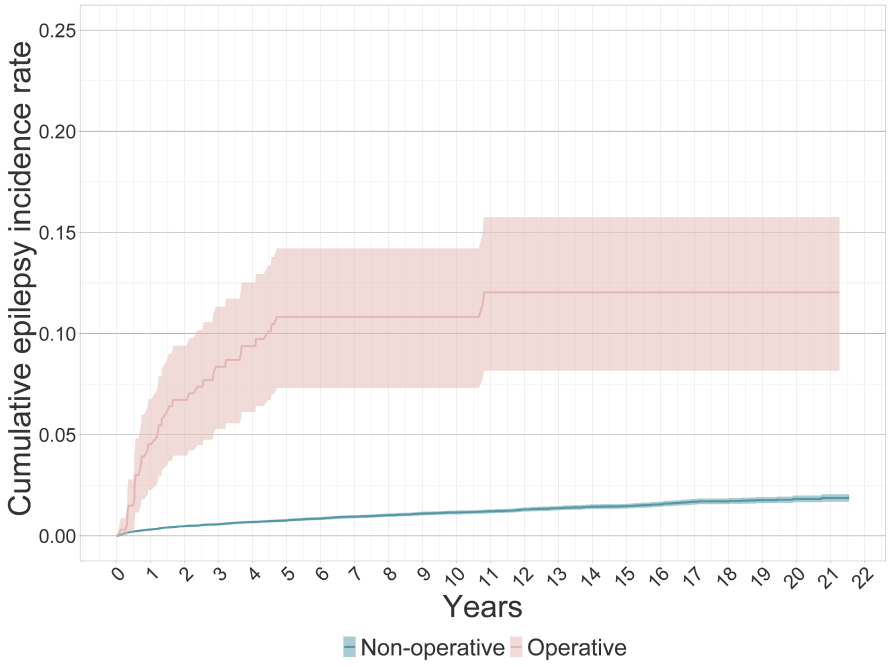

FIGURE 3 Kaplan–Meier curve of the cumulative epilepsy incidence rate between operated and nonoperated patients with 95% confidence intervals for pediatric traumatic brain injury in Finland from 1998 to 2018.

TABLE 4 Kaplan–Meier table of cumulative incidence of epilepsy at 1–15 years post-pTBI in operatively and nonoperatively managed patients.

		At 1 year		At 4 years		At 10 years		At 15 years	
	N.of	*n*.risk	Cumulative incidence (CI)	*n*.risk	Cumulative incidence (CI)	*n*.risk	Cumulative incidence (CI)	*n*.risk	Cumulative incidence (CI)
Operative	337	310	4.5% (2.3–6.7)	257	9.4% (6.1–12.5)	164	10.8% (7.3–14.2)	84	12.0% (8.2–15.8)
Nonoperative	71 632	66 295	.3% (.3–.4)	51 076	.7% (.6–.7)	29 784	1.2% (1.1–1.2)	16 702	1.5% (1.4–1.6)

Abbreviations: CI, confidence interval; *N*.of, number of patients; *n*.risk, number at risk; pTBI, pediatric traumatic brain injury.

meta-analysis consisted of 19 studies with relatively small cohorts, whereas our study consisted of almost 72 000 patients with pTBI. Therefore, our results have better statistical power.[5] A Finnish cohort study of 290 patients with pTBI who were treated in intensive care units reported that the incidence of PTE was 20% and the median time to antiseizure medication purchases for epilepsy after TBI was 125 days. Those patients later diagnosed with clinical epilepsy underwent more intensive management (27% vs. 5%), and patients with low Glasgow Coma Scale scores[3–8] had higher odds for developing PTE.[22]

Adult PTE is a more widely studied subject, and the estimation of PTE is between 3% and 5% after moderate TBI and between 25% and 50% after severe TBI.[23] Approximately 5% of incident cases and 20% of prevalent cases in the epilepsy population are considered to be due to previous TBI.[11] A German cohort study of more than 100 000 patients studied how TBI treatment intensity affected late sequalae and found an incidence rate ratio of 4.19 for severe TBI-related PTE.[24]

PTE is a major complication of pTBI and may degrade the patient's quality of life. It is, therefore, crucial to identify those patients at risk for TBI and to consider long-term posttraumatic surveillance. Even in cases of mild TBI, the risk for PTE is especially high for the first 2 years after trauma. Furthermore, recent studies indicate that the incidence of pTBI is drastically increasing.[8]

Our study has several strengths. Of these, the main strength is the high quality of the registers included in the study.[25–27] ICD-10 classification has been used in Finland since 1998, and the coding measures have remained similar throughout the study period. Studies based on the Finnish Care Register for Health Care using ICD-10 coding and Finnish Social Insurance Institution data have previously been made in neurological[28,29] and cardiovascular diseases.[30] Another strength is the free specialized health care visits for children in Finland. The costs of the health care visit are covered by the social insurance system, which is financed by the universal social insurance fees that every permanent resident of Finland is obligated to pay according to their yearly income.[31] Both the high-quality registers and the reimbursement system are provided by the Finnish national health care system and serve to enable qualified register studies. A further strength of our study is the large study population of more than 70 000 patients with pTBI, which is larger than the total number of patients in the previous meta-analysis of 19 studies combined. A final strength of the study was the use of special reimbursement codes collected from the Finnish Social Insurance Institution. The Finnish Social Insurance Institution has very strict criteria for medicine reimbursement, and the process requires the confirmation of epilepsy by a pediatric neurologist. This means that all the diagnoses of epilepsy in our study population are precise and reliable.

This study has some weaknesses that should be addressed. First, the Finnish Care Register for Health Care does not contain information about the family history of patients. Therefore, the effect of epilepsy genetics could not be analyzed.[32] The Finnish Care Register for Health Care also lacks information on the race, ethnicity, and region of patients. Second, the registry data may include diagnostic errors based on the coding of the pTBI diagnoses performed by clinicians. Third, the study data do not contain information from primary care. As mild injuries are often managed by primary care providers, the rate of milder injuries is likely to have been underestimated in this study. Fourth, the registers used in this study did not include Glasgow Coma Scale ratings or other severity ratings, such as duration of posttraumatic amnesia. The study group assumed that operatively managed pTBI patients had a high-impact injury and, therefore, had a more severe TBI. It should be emphasized that in some cases originally moderate TBI could have later caused complications that may have required operative intervention. Fifth, the study data included only the first TBI. Therefore, cumulative risk of multiple TBI injuries of various severities and related epilepsy could not be evaluated from our register data. Furthermore, our study did not consider other factors that could have affected the incidence of epilepsy. For example, not only may PTE be injury-related, but due to posttraumatic neuroinflammation, TBI can be a triggering effect in the pathway of epileptogenesis.[33] Finally, only the special reimbursement codes of the Finnish Social Insurance Institution were used for epilepsy diagnoses. As a result, the severity of epilepsy could not be evaluated. Information on antiseizure medication purchases was also not available.

In the future, research could examine how different posttraumatic management options for TBI affect the incidence of epilepsy at a later age and whether some management options could be superior in decreasing the incidence of PTE. According to the findings of previous studies of pTBI-related epilepsy, the incidence of epilepsy is approximately 10%, indicating that PTE is a major long-term complication.[14] Therefore, more research on severe TBI-related epilepsy and operative management options and their effect on pediatric epilepsy is needed.

5 | CONCLUSIONS

The results of this large nationwide cohort study demonstrate that pTBI exposes the patient to increased risk of PTE for many years after initial trauma. The risk is especially high for the first 2 posttraumatic years. Moreover,

those children who undergo operative management for TBI have the highest risk for epilepsy, especially in the first 4 years after injury. Our results provide directional information on the importance of TBI prevention and how long-term posttraumatic surveillance or management can affect PTE severity and even incidence.

AUTHOR CONTRIBUTIONS

Ilari Kuitunen, Ville M. Mattila, and Ville Ponkilainen conceptualized the study. Juho Laaksonen and Julius Möttönen conducted the data analysis. Juho Laaksonen drafted the first version of the manuscript. All authors participated in commenting on the manuscript and have approved the final version to be submitted.

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CONFLICT OF INTEREST STATEMENT

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

PATIENT CONSENT STATEMENT

According to Finnish research legislation (Law on Medical Research and Law on the Secondary Use of Routinely Collected Health Care Data), patient consent is not required when the participants in retrospective register studies are not contacted.

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