

# Posttraumatic epilepsy in intensive care unit–treated pediatric traumatic brain injury patients

Era D. Mikkonen<sup>1,2\*</sup> | Markus B. Skrifvars<sup>2</sup> | Matti Reinikainen<sup>3</sup> | Stepani Bendel<sup>3</sup> | Ruut Laitio<sup>4</sup> | Sanna Hoppu<sup>5</sup> | Tero Ala-Kokko<sup>6</sup> | Atte Karppinen<sup>7</sup> | Rahul Raj<sup>7\*</sup>

<sup>1</sup>Department of Anesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital & University of Helsinki, Helsinki, Finland

<sup>2</sup>Department of Emergency Care and Services, Helsinki University Hospital & University of Helsinki, Helsinki, Finland

<sup>3</sup>Department of Anaesthesiology and Intensive Care, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland

<sup>4</sup>Department of Intensive Care, Turku University Hospital and University of Turku, Turku, Finland

<sup>5</sup>Emergency Medical Services, Department of Intensive Care, Tampere University Hospital & Tampere University, Tampere, Finland

<sup>6</sup>Division of Intensive Care, Medical Research Center Oulu MRC, Oulu University Hospital, Research Group of Anesthesiology, Surgery and Intensive Care Medicine, University of Oulu, Oulu, Finland

<sup>7</sup>Department of Neurosurgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

## Correspondence

Era D. Mikkonen, Hölländargatan 31, 11359, Stockholm, Sweden.

Email: era.mikkonen@helsinki.fi

## Funding information

Medicinska Understödsföreningen Liv och Hälsa; Finska Läkaresällskapet

## Abstract

**Objective:** Posttraumatic epilepsy (PTE) is a well-described complication of traumatic brain injury (TBI). The majority of the available data regarding PTE stem from the adult population. Our aim was to identify the clinical and radiological risk factors associated with PTE in a pediatric TBI population treated in an intensive care unit (ICU).

**Methods:** We used the Finnish Intensive Care Consortium database to identify pediatric (<18 years) TBI patients treated in four academic university hospital ICUs in Finland between 2003 and 2013. Our primary outcome was the development of PTE, defined as the need for oral antiepileptic medication in patients alive at 6 months. We assessed the risk factors associated with PTE using multivariable logistic regression modeling.

**Results:** Of the 290 patients included in the study, 59 (20%) developed PTE. Median age was 15 years (interquartile range [IQR] 13–17), and 80% had an admission Glasgow Coma Scale (GCS) score  $\leq 12$ . Major risk factors for developing PTE were age (adjusted odds ratio [OR] 1.08, 95% confidence interval [CI] 1.00–1.16), obliterated suprasellar cisterns (OR 6.53, 95% CI 1.95–21.81), and an admission GCS score of 9–12 in comparison to a GCS score of 13–15 (OR 2.88, 95% CI 1.24–6.69).

**Significance:** We showed that PTE is a common long-term complication after ICU-treated pediatric TBI. Higher age, moderate injury severity, obliterated suprasellar cisterns, seizures during ICU stay, and surgical treatment are associated with an increased risk of PTE. Further studies are needed to identify strategies to decrease the risk of PTE.

## KEYWORDS

epilepsy, intensive care unit, pediatric, traumatic brain injury

\*Conducted the statistical analysis.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Epilepsia* published by Wiley Periodicals, Inc. on behalf of International League Against Epilepsy

## 1 | INTRODUCTION

Traumatic brain injury (TBI) is a common cause of mortality and morbidity in the pediatric population.<sup>1,2</sup> In addition to multiple cognitive, social, and behavioral sequelae, posttraumatic epilepsy (PTE) is a well-described, long-term complication of TBI, and one of the most common causes for acquired epilepsy in both the pediatric and adult population.<sup>3</sup> PTE may have severe consequences on the quality of life and neuropsychological functions of young patients.<sup>4,5</sup> Even if remission is achieved in adulthood, social and educational problems may persist. If seizure remission is not achieved, this group of patients has an increased risk of early death in comparison to their peers.<sup>6</sup> Epileptogenesis after brain insult is a complex series of events, affected by multiple factors, such as age, genetic and lifestyle factors, and previous morbidity. After the injury, processes, including inflammation, blood-brain barrier disruption, parenchymal loss, and neural plasticity, among many others, seem to affect the development of epilepsy.<sup>7</sup> Some evidence suggests that seizure frequency is higher and treatment failure more common in children with acquired epilepsy than in children with congenital epilepsy.<sup>7</sup> Furthermore, drug resistance seems to be especially prevalent in epilepsy following traumatic and diffuse brain injury, and early prophylactic treatment with antiepileptics does not seem to reduce the risk of later development of epilepsy.<sup>8</sup>

Most of the data on PTE have been obtained from adult patients. In both adults and children, brain injury severity is considered to be a risk factor for PTE.<sup>9-11</sup> The risk for PTE seems to correlate with radiological findings, such as subdural hematomas, contusions, and skull fractures.<sup>9,11-15</sup> The onset of PTE may be delayed for years, or even decades. Patients with mild TBI may have an increased risk of epilepsy more than 10 years after the initial insult,<sup>11,15</sup> and patients with more severe intracranial pathologies have an increased risk up to 20 years after sustaining TBI.<sup>9</sup> Although the features of TBI are similar in adults and children, there are some differences. Different developmental phases of the young brain make the pediatric TBI population heterogenic.<sup>16</sup> Consequently, the role of increased neural plasticity in early childhood has been debated.<sup>17</sup> Regarding PTE, the risk of early seizures seems to be higher in the younger population,<sup>14</sup> whereas late seizures seem to be more common in older children.<sup>11</sup>

We aimed to assess the clinical and radiological factors associated with PTE in pediatric TBI patients initially treated in an intensive care unit (ICU) after injury. We also assessed the association between treatment-related factors and PTE. We hypothesized that clinical and radiological evidence indicating a more severe TBI would be associated with a higher risk of PTE.

### Key Points

- We used a national intensive care unit (ICU) database to identify 290 pediatric traumatic brain injury (TBI) patients treated at four university hospital ICUs between 2003 and 2013
- Using ICU data, electronic health records, computed tomography (CT) scans, and national drug reimbursement registries, we investigated the risk factors for posttraumatic epilepsy
- One-fifth of patients developed seizures during follow-up
- Older age, moderate injury severity, and obliterated suprasellar cisterns increase the risk of posttraumatic epilepsy
- Early medical treatment of seizures and surgical treatment of TBI was independently associated with posttraumatic epilepsy

## 2 | METHODS

### 2.1 | Study ethics and standard protocol

The research committee of Helsinki University Hospital (HUS/26/2018 §37), the Finnish National Institute for Health and Welfare (THL/2014/5.05.00/2017), Statistics Finland (TK-53-1047-14), and all of the participating university hospitals approved this study and waived the need for informed consent. We conducted the study according to the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines (Appendix S1).<sup>18</sup>

### 2.2 | Study setting

We used data from the prospective Finnish Intensive Care Consortium (FICC) database.<sup>19</sup> Finland has a three-tier level healthcare system in which intracranial neurosurgery and neurointensive care is provided at only five university hospitals. Four of the five ICUs providing neurointensive care, covering approximately two-thirds of the population, participate in the FICC. All four centers have separate neonatal ICUs admitting children younger than 1 year of age, and three centers have separate pediatric ICUs. Neonatal and pediatric ICUs do not participate in the FICC. However, during the study period, all four centers admitted pediatric TBI patients requiring neurointensive care to the general ICU.

## 2.3 | Study population

Based on Acute Physiology and Chronic Health Evaluation (APACHE) III and International Classification of Diseases, 10th Revision (ICD-10) diagnoses, we identified all patients younger than 18 years of age who were treated for TBI between 2003 and 2013 in the ICUs of the hospitals participating in the study. We extracted relevant ICU data from the FICC database, and we reviewed electronic health records and radiological images to confirm and specify the presence of a TBI with a blunt mechanism. We excluded all patients with missing baseline data, penetrating head injuries, and missing follow-up data, as well as patients with a preexisting epilepsy medication.

## 2.4 | Extracted variables

From the FICC database, we retrieved ICU-related variables (Therapeutic Intervention Scoring System 76 [TISS], length of stay, interventions, administration of antiepileptic drugs). The FICC includes a TISS-76 variable capturing the medical treatment of a new seizure in the ICU that has been clinically diagnosed or confirmed by electroencephalography (EEG) (does not include prophylactic administration of antiepileptic drugs). We retrieved admission variables, such as Glasgow Coma Scale (GCS) scores and pupillary reactivity status, from electronic health records. For intubated patients, we used the GCS score before intubation; we used the pediatric GCS for patients younger than the age of 2.<sup>20</sup> We re-reviewed all computerized tomography (CT) scans and classified them according to the Helsinki CT score (Table S1).<sup>21</sup> We used previously presented criteria for major extracranial injury.<sup>22</sup>

## 2.5 | Definition of outcome variables

Our primary outcome was the development of PTE, defined as the need for oral antiepileptic medication in patients alive at 6 months after experiencing TBI. A patient was defined as having PTE if he/she was being reimbursed for an oral antiepileptic drug (ATC code NO3A\*) by the Social Insurance Institution (Kela). We obtained data on antiepileptic medication reimbursement through the Kela database, which covers all Finnish residents who are reimbursed for antiepileptics and other medications.<sup>23,24</sup> Because time of antiepileptic medication purchase may not accurately capture the time of PTE onset, we only used it as a dichotomic variable (PTE, no PTE).

We assessed functional outcome at 6 months based on the electronic health record data recorded by neuropsychologists, pediatricians, pediatric neurologists, or neurosurgeons. We categorized functional outcome according to the Glasgow

Outcome Scale (GOS), adjusted for age,<sup>25</sup> as follows: favorable functional outcome (GOS 4-5, low disability to good recovery) and unfavorable functional outcome (GOS 1-3, death, persistent vegetative state, and severe disability). Patients whose follow-up ended before 6 months due to no noticeable disability were classified as having reached a favorable functional outcome. For deceased patients, we obtained the dates of deaths from the Population Register in Finland (available for all Finnish citizens).

## 2.6 | Statistical analyses

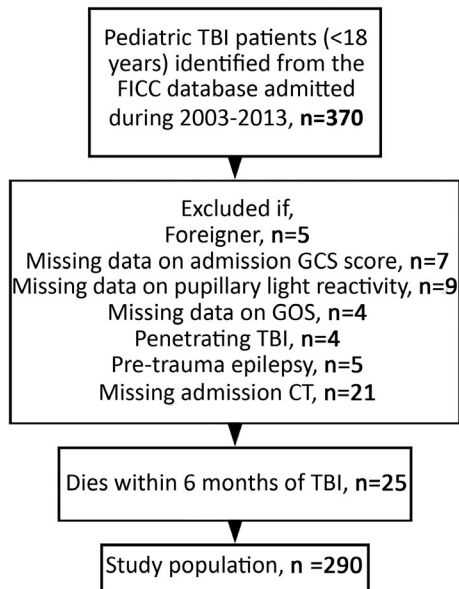
We used SPSS statistical software, version 25.0 for Mac OS (IBM Corp) for all statistical analyses. We used a two-sided  $\chi^2$ -test to compare the categorical data, and we tested the continuous data for skewness. We present normally distributed data as means with standard deviations (SDs); we present the non-parametric data as medians with interquartile ranges (IQR). We used a *t* test to compare the normally distributed data between groups, and we used a nonparametric Mann-Whitney *U* test to compare the nonparametric data between groups.

We assessed the factors independently associated with PTE using multivariable logistic regression (LR) analysis. We included variables from the univariate analysis with an associated *P*-value of <.10 in the multivariable LR models to identify the independent risk factors for PTE. We created a clinical LR model and a separate radiological LR model. Then, we tested the clinical and radiological variables in a final LR model, including variables from previous LR models that had a *P*-value <.1 (combined model). As a secondary analysis, we tested the association between treatment-related factors and the risk of PTE by adding treatment-related variables to an LR model. We determined multicollinearity by assessing and reporting the maximal variance inflation factor ( $VIF_{max}$ ).

## 3 | RESULTS

Of 315 patients, 25 patients died within 6 months. Thus, the study population consisted of 290 patients (Figure 1). Median follow-up time was 3.4 years (interquartile range [IQR] 1.2-6.3 years). Of the 290 patients, 59 (20%) developed PTE. Median time for purchase of an oral antiepileptic drug after TBI was 125 days (IQR 26-601). Of the patients with PTE, 81% had a favorable GOS after 6 months, in comparison to 91% of the patients without PTE (*P* = .037).

The baseline characteristics of the patients are presented in Table 1. Patients who developed PTE were slightly older (median age 15 vs 13, *P* = .002) than the patients who did not develop PTE; they also had a lower GCS score (median



**FIGURE 1** Flow chart showing the included and excluded patients. Abbreviations: CT, computerized tomography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; TBI, traumatic brain injury

8 vs 12,  $P = .004$ ), more often had abnormal pupillary light reactivity (24% vs 10%,  $P = .01$ ), and had more CT-detected intracranial lesions. Furthermore, patients developing PTE underwent more intensive treatment by interventions, such as decompressive craniectomy (27% vs 5%,  $P < .001$ ), parenchymal intracranial pressure (ICP) monitoring (56% vs 26%,  $P < .001$ ), repeated use of barbiturates (24% vs 7%,  $P < .001$ ), antiepileptic treatment (46% vs 13%,  $P < .001$ ), higher TISS-76 scores, and longer length of stay in the ICU (median 4 days vs 1 day,  $P < .001$ ).

The differences according to GCS score groups are shown in Table S2. Patients with a higher GCS score were younger than those with a lower GCS score; they more often had normal pupillary light responses and they had more acute subdural hematomas and epidural hematomas; however, they less frequently experienced traumatic subarachnoid hemorrhage and intraventricular hemorrhage. Almost two-thirds of patients were victims of traffic accidents, including pedestrian, bicycle, moped, and car accidents (Table S3). Moped accident was the single most common injury mechanism and accounted for 25% of all patients. Fall from height was the most common nontraffic injury mechanism (16%).

### 3.1 | Multivariable analyses

In the clinical model, we included age, GCS score, and pupillary light reactivity (Table 2). All these variables increased the risk of PTE in the univariate analyses with a  $P$ -value  $< .1$ . Still, in the clinical model, only the admission GCS scores

of 3-8 and 9-12 independently increased the risk for PTE ( $P < .05$ ). The  $VIF_{\max}$  in the clinical model was 1.31.

Of the six radiological factors that were investigated, only obliterated suprasellar cisterns and the presence of brain contusions independently increased the risk of PTE (Table 3). The  $VIF_{\max}$  in the radiological model was 2.09.

In the combined clinical and radiological LR model (Table 4), only age, a GCS score of 9-12, and obliterated suprasellar cisterns remained statistically significant predictors of PTE. The  $VIF_{\max}$  in the combined model was 1.39.

### 3.2 | Treatment-related interventions

After including treatment-related factors in a model consisting of age, the following significantly increased risk of PTE: GCS score, craniotomy or decompressive craniectomy, and medical treatment for a new seizure in the ICU (Table 5). The use of a parenchymal ICP monitor or an external ventricular drain (EVD), or the repeated use of barbiturates did not increase the risk of PTE. The  $VIF_{\max}$  in this model was 1.75.

## 4 | DISCUSSION

In this retrospective multicenter observational study, we assessed the risk factors associated with PTE in pediatric TBI survivors treated in the ICU over an 11-year period. We found that obliterated suprasellar cisterns on the admission head CT scan, an impaired level of consciousness on admission, and increasing age were associated with an increased risk of PTE. We also found that craniotomy or decompressive craniectomy and medical treatment for early seizures in the ICU were associated with an increased risk of PTE. Moreover, patients who developed PTE also had higher rates of unfavorable functional outcome.

At the beginning of the study period in 2003, the incidence of epilepsy in Finland was 62.1/100 000 in the 0- to 15-year-old age group; thus, 0.06% of this population developed epilepsy that year. In our population, as expected, the incidence was significantly higher at 2% per year.<sup>24</sup>

Forty-three percent of our cohort had mild TBI (GCS 13-15). In a multicenter trial of the adult population treated in the ICU, 36% had mild TBI.<sup>26</sup> The slightly higher count in our cohort could be explained by cautionary measures when treating children and adolescents. Previous studies have reported a positive correlation between higher TBI severity and an increased risk of PTE in children. However, it is less clear if the admission GCS score is a reliable marker of TBI severity, and, thus, the risk of PTE.<sup>10,14,27</sup> In our study, we could not find a strong linear relationship between the admission GCS score and the risk of PTE. When the clinical and radiological factors were combined,

**TABLE 1** Patient characteristics according to posttraumatic epilepsy

Clinical variables	All (n = 290)	PTE (n = 59)	No PTE (n = 231)	P-Value
Age, median (IQR)	14 (9-16)	15 (13-17)	13 (8-16)	.002
0-5	43 (15%)	5 (8%)	38 (16%)	.001
6-12	78 (27%)	7 (12%)	71 (31%)	
13-17	169 (58%)	47 (80%)	122 (53%)	
Females	87 (30%)	14 (24%)	73 (32%)	.24
GCS score, median (IQR)	11 (6-14)	8 (6-12)	12 (6-15)	.004
3-8	105 (36%)	30 (51%)	75 (33%)	<.001
9-12	61 (21%)	17 (29%)	44 (19%)	
13-15	124 (43%)	12 (20%)	112 (48%)	
Pupillary light reactivity				
Both react	254 (88%)	45 (76%)	209 (90%)	.01
One reacts	27 (9%)	10 (17%)	17 (8%)	
None react	9 (3%)	4 (7%)	5 (2%)	
Major extracranial injury	110 (38%)	25 (42%)	85 (37%)	.43
Treatment-related variables				
Rx of new seizure in the ICU	56 (19%)	27 (46%)	29 (13%)	<.001
Craniotomy	57 (20%)	14 (24%)	43 (19%)	.38
Decompressive craniectomy	28 (10%)	16 (27%)	12 (5%)	<.001
Parenchymal ICP monitoring	81 (28%)	33 (56%)	59 (26%)	<.001
External ventricular drain	15 (5%)	4 (7%)	11 (5%)	.53
Repeated use of barbiturates	31 (11%)	14 (24%)	17 (7%)	<.001
TISS-76 mean per day (median, IQR)	24 (19-34)	32 (23-38)	22 (18-32)	<.001
TISS-76 total (median, IQR)	62 (37-305)	157 (62-523)	50 (34-2214)	<.001
LOS ICU, (median, IQR)	2 (1-8)	4 (1-12)	1 (1-6)	<.001
LOS hospital, (median, IQR)	8 (5-19)	19 (8-39)	7 (5-15)	<.001
Radiological variables				
ASDH	84 (29%)	23 (39%)	61 (26%)	.06
Contusion/traumatic ICH	163 (56%)	41 (69%)	122 (53%)	.02
EDH	51 (18%)	10 (17%)	41 (18%)	.89
Mass lesion >25 cc	27 (9%)	10 (17%)	17 (7%)	.02
tSAH	91 (31%)	25 (42%)	66 (29%)	.04
IVH	37 (13%)	11 (19%)	26 (11%)	.13
Suprasellar cisterns				
Normal	242 (83%)	40 (68%)	202 (87%)	<.001
Compressed	32 (11%)	9 (15%)	23 (10%)	
Obliterated	16 (6%)	10 (17%)	6 (3%)	
Midline shift >5 mm	27 (9%)	11 (19%)	16 (7%)	.006
Helsinki CT score, median (IQR)	2 (0-4)	2 (2-5)	2 (0-3)	.001

Note: Values are presented as the number (%) of patients or as the median (IQR).

Abbreviations: ASDH, acute subdural hematoma; CT, computerized tomography; EDH, epidural hematoma; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; ICP, intracranial pressure; ICU, intensive care unit; IQR, interquartile range; IVH, intraventricular hematoma; LOS, length of stay; PTE, posttraumatic epilepsy; Rx, medical treatment; TISS, Therapeutic Intervention Scoring System; tSAH, traumatic subarachnoid hemorrhage.

patients with moderate TBI (GCS 9-12) had an increased risk for PTE in comparison to patients with mild TBI (GCS 13-15). Patients with severe TBI (GCS 3-8) did not display

an increased risk for PTE in comparison to those with mild TBI. Similar to our results, a study on adult TBIs found that an admission GCS of 9-12 is associated with the highest

**TABLE 2** Results from the logistic regression model of clinical factors

Clinical variables	Odds ratio (95% CI)	P-value
Age, years	1.07 (1.00-1.15)	.06
GCS score		
13-15	1.0 (reference)	
9-12	3.25 (1.42-7.43)	.005
3-8	2.44 (1.07-5.57)	.03
Pupillary light reactivity		
Normal	Reference	
One reacts/none react	0.48 (0.20-1.14)	.10

Abbreviation: GCS, Glasgow Coma Scale.

risk of PTE.<sup>28</sup> However, the reasons for this are unclear. In our cohort, there were no major differences in the radiological parameters between the patients with a GCS of 9-12 and those with a GCS of 3-8 (Table S2). It is possible that the strong correlation between a low GCS score and high 6-month mortality masks the association between a low GCS score and PTE, as some of the patients who would have developed PTE died. Yet, it is possible that the null finding between a GCS of 3-8 and the risk of PTE is a consequence of lack of statistical power.

In our cohort, approximately 10% of patients with mild TBI (GCS 13-15) developed PTE. In comparison, a previous study on pediatric patients with mild TBI reported a PTE rate of 4%.<sup>29</sup> The difference is probably explained by a higher rate of abnormal brain imaging findings in our cohort (more intracranial hemorrhages and signs of brain edema). Thus, the high incidence of traumatic intracranial pathologies in our mild TBI cohort is most likely the reason for the perhaps surprisingly high incidence of PTE in this subgroup.

Many large studies focusing on adult and pediatric TBI have investigated the relationship between intracranial pathologies and PTE. A systematic review of the adult literature found skull fractures, midline shift, contusions, and subdural and intracerebral hematomas to associate with the risk of PTE.<sup>15</sup> Large pediatric studies have found risk factors to include subdural hematomas and contusions.<sup>11,12</sup> These findings were not supported by our data. When assessing radiological risk factors separately, contusions showed a statistically significant association with PTE, but this association disappeared when adjusting for clinical variables. In contrast to defining intracranial pathologies using diagnostic coding (eg, by ICD diagnostic codes), we reviewed the CT scans, which allowed us to extract more nuanced information about intracranial pathologies. This could explain the conflict with some previous studies. For example, we found that the obliterated suprasellar cisterns had the strongest association with PTE of all the analyzed factors in our data. Suprasellar cistern status has been demonstrated to be a strong indicator of TBI

**TABLE 3** Results from the logistic regression model of radiological factors

Radiologic variables	Odds ratio (95% CI)	P-value
ASDH		
No	1.0 (reference)	
Yes	1.10 (0.53-2.27)	.80
Contusion		
No	1.0 (reference)	
Yes	2.21 (1.10-4.46)	.03
Mass lesion >25 cc		
No	1.0 (reference)	
Yes	1.71 (0.49-5.97)	.40
Suprasellar cisterns		
Normal	1.0 (reference)	
Compressed	1.26 (0.45-3.48)	.66
Obliterated	4.32 (1.05-17.76)	.04
Midline shift, >5 mm		
No	1.0 (reference)	
Yes	1.55 (0.43-5.61)	.50
tSAH		
No	1.0 (reference)	
Yes	1.31 (0.67-2.59)	.43

Abbreviations: ASDH, acute subdural hematoma; tSAH, traumatic subarachnoid hemorrhage.

injury severity, and consequently a strong prognostic marker of poor general outcome.<sup>21</sup> Obliteration of the suprasellar cisterns is a sign of severe diffuse injury and swelling, and, as noted before, diffuse brain injury has been associated with drug-resistant PTE.<sup>7</sup>

In our study, increasing age was associated with an increased risk of PTE. This is in line with a large Danish population-based study, which found a slight increase in the risk of PTE with increasing age in a large pediatric cohort.<sup>11</sup> They reported a linear relationship between the risk of PTE and age in mild TBI, whereas the relationship was U-shaped in cases with more severe TBI. Yet, due to the relatively low number of very young patients in our cohort, we were unable to observe this.

In a secondary analysis, looking at the association between treatment-related variables and risk of PTE, we found a significantly increased risk for PTE in patients who underwent either craniotomy or decompressive craniectomy. In the adult TBI literature, Englander et al found an increased risk of PTE in adult TBI patients with acute subdural hematoma who underwent craniotomy vs no intervention.<sup>28</sup> Previous studies regarding pediatric TBIs have found that that 20%-33% of pediatric TBI patients undergoing craniectomy later develop PTE.<sup>30,31</sup> In comparison, 57% of all patients undergoing decompressive craniectomy in our cohort later

**TABLE 4** Results from the combined logistic regression model of clinical and radiological factors

Clinical variables	Odds ratio (95% CI)	P-value
Age, y	1.08 (1.00-1.16)	.04
GCS score		
13-15	1.0 (reference)	
9-12	2.88 (1.24-6.69)	.01
3-8	1.84 (0.78-4.36)	.16
Pupillary light reactivity		
Normal	1.0 (reference)	
One reacts/none react	0.68 (0.26-1.77)	.43
Contusion		
No	1.0 (reference)	
Yes	1.61 (0.83-3.15)	.16
Suprasellar cisterns		
Normal	1.0 (reference)	
Compressed	1.93 (0.80-4.70)	.15
Obliterated	6.53 (1.95-21.81)	.002

Abbreviation: GCS, Glasgow Coma Scale.

developed PTE. Apart from the underlying brain insult necessitating intervention, a possible epileptogenic mechanism in craniectomy could be parenchymal tear when brain tissue is allowed to swell and stretch. In contrast to adult TBI, we did not find an association between the use of EVD or parenchymal ICP measuring devices and PTE.<sup>28</sup> Furthermore, in line with previous studies, we found an association between early seizures or epileptiform activity (medical treatment of a new seizure in the ICU) and the risk of PTE.<sup>10,14,32</sup> However, given the study design, it is not possible to draw conclusions as to whether the increased risk of PTE is due to the underlying brain pathology leading to the intervention or due to the intervention itself. Thus, this secondary analysis should be interpreted with caution.

Epileptogenesis after brain insult is a complex cascade of events, and although preclinical animal models have shown some evidence in support of prophylactic measures to prevent PTE, such as high-dose losartan,<sup>33</sup> no treatments have been proven to be effective in humans.<sup>7,8</sup>

To ensure that future interventional studies are safe and effective, it is necessary to identify patients at high risk for PTE; otherwise patients run the risk of being exposed to unnecessary treatments, which can be harmful to young, developing brains.<sup>34,35</sup> We believe that our work can provide future studies with better tools for improved patient selection and baseline risk stratification.

Our study has several strengths. It includes four university hospital ICUs over a 11-year study period. All data were retrieved directly through electronic health records or from the FICC and Kela databases, securing high quality data.<sup>19,36</sup> Furthermore, we independently reviewed all the

**TABLE 5** Association between treatment-related interventions and posttraumatic epilepsy after adjusting for significant clinical and radiological variables

Variable	Odds ratio (95% CI)	P-value
Age	1.08 (1.00-1.17)	.04
GCS score		
13-15	1.0 (reference)	
9-12	2.66 (1.09-6.49)	.03
3-8	1.59 (0.64-3.97)	.32
Suprasellar cisterns		
Normal	1.0 (reference)	
Compressed	1.13 (0.42-3.06)	.81
Obliterated	3.52 (0.95-13.01)	.06
Rx of new seizure in the ICU	3.41 (1.57-7.43)	.002
Craniotomy or decompressive craniectomy		
Craniotomy or decompressive craniectomy	2.14 (1.02-4.47)	.04
Parenchymal ICP monitor or EVD		
Parenchymal ICP monitor or EVD	1.07 (0.56-2.52)	.87
Repeated use of barbiturates		
Repeated use of barbiturates	1.70 (0.61-4.74)	.31

Abbreviations: EVD, external ventricular drain; GCS, Glasgow Coma Scale; ICP, intracranial pressure; ICU, intensive care unit; Rx, medical treatment; Rx, treatment.

patients' CT data, allowing us to examine the effects of lesion size, midline shift, suprasellar cistern status, and intraventricular hemorrhage, which are factors that are missed in register studies that use diagnostic coding to identify pathology.

However, the study has some limitations. Although including four academic university hospitals, together covering two-thirds of the Finnish population, the size of our cohort was relatively small due to the rarity of pediatric TBI in Finland. Thus, we had to combine some of the clinically related variables instead of analyzing them separately (eg, craniotomy and decompressive craniectomy, EVD, and intraparenchymal ICP device). The baseline characteristics of 41 patients were missing; thus, they were excluded from the study. As described previously, all of the included centers admitted pediatric patients requiring neurointensive care after TBI to their ICUs.<sup>21</sup> Thus, according to the treatment protocols, all patients with severe TBI were included in our study. Some patients with a less-severe TBI might have been admitted to the neonatal ICU (age < 1 year) or the pediatric ICU (age 1-16 years); thus, they were not included in the study. This could explain the lack of infants with inflicted trauma ("shaken baby syndrome") in our data; thus, our results are not generalizable to these patients. Finally, purchase of oral antiepileptic medication is

a crude measure of epilepsy. As oral medication provided in other hospitals is not captured by our data, this makes estimation of actual onset of disease difficult to estimate. However, we consider it reliable at capturing long-term disease.

## 5 | CONCLUSION

Posttraumatic epilepsy is a common long-term complication in ICU-treated pediatric TBI survivors. Older age, moderate injury severity, and obliterated suprasellar cisterns were associated with an increased risk of PTE. Early medical treatment of seizures and operative treatment of TBI was independently associated with PTE. Future multinational collaborative studies that identify more detailed patient-specific and injury-specific factors related to PTE are warranted.

## ACKNOWLEDGMENTS

We would like to thank Medicinska Understödsföreningen Liv & Hälsa and Finska Läkaresällskapet for the funding of this study.



## CONFLICT OF INTERESTS

Era Mikkonen, Matti Reinikainen, Stepani Bendel, Ruut Laitio, Tero Ala-Kokko, and Atte Karppinen: No separate funding. Markus Skrifvars: Independent funding from University of Helsinki, Helsinki University Hospital, Medicinska Understödsföreningen Liv & Hälsa, Dorothea Olivia, Karl Walter och Jarl Walter Perklens stiftelse. Sanna Hoppu: Competitive State Research Financing of Tampere University Hospital. Rahul Raj: Independent funding from Medicinska Understödsföreningen Liv & Hälsa, Finska Läkaresällskapet, Svenska Kulturfonden, Helsinki University Hospital research grant. None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## DATA AVAILABILITY STATEMENT

Due to data sensitivity and Kela and THL legislation, sharing is not applicable. Data can be requested from the Finnish Intensive Care Consortium, Kela, National Institute for Health and Welfare.

## ORCID

Era D. Mikkonen  <https://orcid.org/0000-0003-1379-0235>  
Rahul Raj  <https://orcid.org/0000-0003-4243-9591>

## REFERENCES

- Appenteng R, Nelp T, Abdelgadir J, Weledji N, Haglund M, Smith E, et al. A systematic review and quality analysis of pediatric traumatic brain injury clinical practice guidelines. *PLOS One*. 2018;13:e0201550.
- Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. *J Neurotrauma*. 2012;29:1717–27.
- Lowenstein DH. Epilepsy after head injury: an overview. *Epilepsia*. 2009;50:4–9.
- Ronen GM, Streiner DL, Rosenbaum P. Health-related quality of life in childhood epilepsy: moving beyond “seizure control with minimal adverse effects”. *Health Qual Life Outcomes*. BioMed Central. 2003;1:36.
- Cianchetti C, Messina P, Pupillo E, Crichiutti G, Baglietto MG, Veggiotti P, et al. The perceived burden of epilepsy: impact on the quality of life of children and adolescents and their families. *Seizure*. 2015;24:93–101.
- Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. *N Engl J Med*. 1998;338:1715–22.
- Klein P, Dingledine R, Aronica E, Bernard C, Blümcke I, Boison D, et al. Commonalities in epileptogenic processes from different acute brain insults: Do they translate? *Epilepsia*. 2018;59:37–66.
- Thompson K, Pohlmann-Eden B, Campbell LA, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst Rev*. 2015;(8):CD009900. Epub 2015 Aug 10.
- Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med*. 1998;338:20–4.
- Appleton RE, Demellweek C. Post-traumatic epilepsy in children requiring inpatient rehabilitation following head injury. *J Neurol Neurosurg Psychiatry*. 2002;72:669–72.
- Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet*. 2009;373:1105–10.
- Rumalla K, Smith KA, Letchuman V, Gandham M, Kombathula R, Arnold PM. Nationwide incidence and risk factors for posttraumatic seizures in children with traumatic brain injury. *J Neurosurg Pediatr*. 2018;22:684–93.
- Petridis AK, Doukas A, Maslehaty H, Mehdorn HM. Predictors and incidence of posttraumatic seizures in children and adolescents after brain injury. *Clin Pract*. 2012;2(3):e66.
- Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia*. 1999;40:584–9.
- Xu T, Yu X, Ou S, Liu XI, Yuan J, Huang H, et al. Risk factors for posttraumatic epilepsy: a systematic review and meta-analysis. *Epilepsy Behav*. 2017;67:1–6.
- Figaji AA. Anatomical and physiological differences between children and adults relevant to traumatic brain injury and the implications for clinical assessment and care. *Front Neurol*. 2017;8:685.
- Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. 2011;134:2197–221.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. Elsevier. 2014;12:1495–9.



19. Reinikainen M, Mussalo P, Hovilehto S, Uusaro A, Varpula T, Kari A, et al. Association of automated data collection and data completeness with outcomes of intensive care. A new customised model for outcome prediction. *Acta Anaesthesiol Scand*. 2012;56:1114–22.
20. Borgialli DA, Mahajan P, Hoyle JD Jr, Powell EC, Nadel FM, Tunik MG, et al. Performance of the pediatric glasgow coma scale score in the evaluation of children with blunt head trauma. *Acad Emerg Med*. 2016;23:878–84.
21. Mikkonen ED, Skrifvars MB, Reinikainen M, Bendel S, Laitio R, Hoppu S, et al. Validation of prognostic models in intensive care unit–treated pediatric traumatic brain injury patients. *J Neurosurg Pediatr*. 2019;24:330–337.
22. Trial CMRCC, Perel P, Arango M, Clayton T, Edwards P, Komolafe E, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ*. 2008;336:425–9.
23. Finnish Statistics on Medicines - kela.fi [online]. Accessed at: [https://www.kela.fi/web/en/statistical-publications\\_finnish-statistics-on-medicines](https://www.kela.fi/web/en/statistical-publications_finnish-statistics-on-medicines). Accessed July 9, 2019.
24. Saarinen MM, Sillanpää M, Schmidt D, Virta LJ. Long-term changes in the incidence of childhood epilepsy. A population study from Finland. *Epilepsy Behav*. 2016;58:81–5.
25. Young AMH, Guilfoyle MR, Fernandes H, Garnett MR, Agrawal S, Hutchinson PJ. The application of adult traumatic brain injury models in a pediatric cohort. *J Neurosurg Pediatr*. 2016;18:558–64.
26. Steyerberg EW, Wieggers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol*. 2019;18:923–34.
27. Keret A, Shweiki M, Bennett-Back O, Abed-Fteiha F, Matoth I, Shoshan Y, et al. The clinical characteristics of posttraumatic epilepsy following moderate-to-severe traumatic brain injury in children. *Seizure*. 2018;58:29–34.
28. Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, et al. Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. *Arch Phys Med Rehabil*. 2003;84:365–73.
29. Keret A, Bennett-Back O, Rosenthal G, Gilboa T, Shweiki M, Shoshan Y, et al. Posttraumatic epilepsy: long-term follow-up of children with mild traumatic brain injury. *J Neurosurg Pediatr*. 2017;20:64–70.
30. Pechmann A, Anastasopoulos C, Korinthenberg R, van Velthoven-Wurster V, Kirschner J. Decompressive craniectomy after severe traumatic brain injury in children: complications and outcome. *Neuropediatrics*. 2014;46:005–12.
31. Kan P, Amini A, Hansen K, White GL, Brockmeyer DL, Walker M, et al. Outcomes after decompressive craniectomy for severe traumatic brain injury in children. *J Neurosurg*. 2006;105:337–42.
32. Kim JA, Boyle E, Wu AC, Cole AJ, Staley KJ, Zafar S, et al. Epileptiform activity in traumatic brain injury predicts post-traumatic epilepsy. *Ann Neurol*. 2018;83:858–862.
33. Bar-Klein G, Cacheaux LP, Kamintsky L, Prager O, Weissberg I, Schoknecht K, et al. Losartan prevents acquired epilepsy via TGF- $\beta$  signaling suppression. *Ann Neurol*. 2014;75:864–75.
34. Ikonomidou C, Turski L. Antiepileptic drugs and brain development. *Epilepsy Res*. 2010;88:11–22.
35. Marsh ED, Brooks-Kayal AR, Porter BE. Seizures and antiepileptic drugs: does exposure alter normal brain development? *Epilepsia*. 2006;47:1999–2010.
36. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic Countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol*. 2010;106:86–94.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Mikkonen ED, Skrifvars MB, Reinikainen M, et al. Posttraumatic epilepsy in intensive care unit–treated pediatric traumatic brain injury patients. *Epilepsia*. 2020;61:693–701. <https://doi.org/10.1111/epi.16483>