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Seizures in Children with Severe Traumatic Brain Injury

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Abstract

Objective—Traumatic brain injury (TBI) causes substantial morbidity and mortality in children. Post-traumatic seizures (PTS) may worsen outcomes after TBI. PTS risk factors are incompletely understood. Our objective was to clarify PTS risk factors in a large cohort of children with severe TBI.

Design—Retrospective cohort study of a probabilistically linked dataset from the National Trauma Data Bank (NTDB) and the Pediatric Health Information Systems (PHIS) database, 2007–2010

Setting—29 U.S. children's hospitals

Patients—2,122 children (age < 18 years old at admission) with linked NTDB and PHIS records, severe (Emergency Department [ED] Glasgow Coma Scale [GCS] < 8) TBI, hospital length of stay > 24 hours, and non-missing disposition

Interventions—None

Measurements and Main Results—The outcome was PTS, identified using validated ICD-9-CM diagnosis codes. Pre-specified candidate predictors of PTS included age, injury mechanism, ED GCS, intracranial hemorrhage type, hypoxia, hypotension, and cardiac arrest. PTS were diagnosed in 25.2% of children with severe TBI. In those without abuse/assault or subdural hemorrhage (SDH), the PTS rate varied between 36.6% in those < 2 years old and 16.4% in those 14–17 years old. Age, abusive mechanism, and subdural hemorrhage (SDH) are each significant predictors of PTS. The risk of PTS has a complex relationship with these predictors. The estimated odds of PTS decrease with advancing age, OR = 0.929 (0.905, 0.954) per additional year of age with no abuse/assault and no SDH; OR = 0.820 (0.730, 0.922) per additional year of age when

abuse and SDH are present. An infant with accidental TBI and SDH has approximately the same estimated probability of PTS as an abused infant without SDH, 47% (95% CI: 39%, 55%) versus 50% (95% CI: 41%, 58%), $P = 0.69$. The triad of young age, injury by abuse/assault, and SDH confers the greatest estimated probability for PTS, 60% (95% CI: 53%, 66%).

Conclusions—PTS risk in children with severe TBI is greatest with a triad of younger age, injury by abuse/assault, and SDH. However, PTS is common even in the absence of these factors.

Keywords

seizures; traumatic brain injury; child abuse; subdural hematoma

Introduction

Over 500,000 children suffer traumatic brain injury (TBI) each year in the United States, resulting in more than 35,000 hospitalizations and greater than 2,000 deaths.(1) Survivors of childhood TBI frequently have long-term physical, academic, behavioral, or social impairments.(2) Factors associated with outcomes include TBI severity, age, injury mechanism, and the extent of secondary cerebral injury, among others. Post-traumatic seizures (PTS) are one factor that may contribute to secondary cerebral injury. PTS are typically classified based on time of occurrence (3, 4): impact seizures occur within minutes after injury, early PTS within 7 days, and late PTS after 7 days. Other than impact seizures, all PTS have been consistently associated with poorer outcomes after TBI (3, 5–8).

PTS may contribute to secondary cerebral injury due to increases in metabolic demands, elevation of intracranial pressure, and release of neurotransmitters.(10, 11) The occurrence of subclinical PTS may be particularly detrimental, as diagnosis and treatment can be difficult.(10, 12, 13) Specific populations of severe TBI victims may be at greater risk for subclinical PTS, including young children injured by abuse/assault.(7, 12, 14)

Reported incidences of PTS in pediatric TBI patients range from 5.5 to 45%(3, 5, 9, 12, 15), likely due to heterogeneity in study populations and designs.(3) Use of continuous electroencephalographic (EEG) monitoring may increase PTS recognition, and PTS rates are higher in studies in which continuous EEG was used.(12–14)

The most commonly identified risk factors for PTS in children are younger age, more severe TBI, subdural hemorrhage (SDH) and abusive mechanism. (5, 9, 14, 16, 17) Multiple risk factors for PTS are frequently present in combination, making determination of individual contributions to overall risk challenging. This is particularly true among young children injured by abuse/assault because young age, SDH, and abusive mechanism frequently occur simultaneously.(7, 18, 19) Previous studies of PTS in children have been limited by sample size in their ability to separate the independent effects of each individual PTS risk factor.

Consensus guidelines for treatment of severe pediatric TBI support antiepileptic drug (AED) prophylaxis for children “at high risk of seizures.”(20) However, determining which children are at highest risk remains challenging. Additionally, further clarification of PTS risk is needed to help guide use of continuous EEG monitoring. The objectives of our study were:

(1) to clarify early predictors for PTS in a very large cohort of infants and children with severe TBI and (2) to determine the effects of age, SDH, and abusive mechanism on PTS risk.

Methods

Data Sources and Cohort Design

Two data sources provided information for this study, the National Trauma Data Bank (NTDB) and the Pediatric Health Information Systems (PHIS) database.

NTDB—The NTDB contains standardized trauma registry data from more than 3 million admissions at 900 trauma centers in the United States.(21) It contains injury and clinical variables necessary for studies of TBI, but does not contain detailed treatment information. The NTDB contains no protected health information (PHI). The NTDB has a continuous data quality improvement process.(21)

PHIS—PHIS is a benchmarking and quality improvement database containing inpatient data from 44 U.S. children's hospitals with more than 500,000 discharges per year.(22) PHIS contains administrative data, diagnoses, and procedures as well as utilization information for pharmacy, imaging, laboratory, supply, nursing, and therapy services. PHIS data are only available to approved researchers at member hospitals and do contain limited PHI (complete dates of birth, admission, and discharge, and a hospital identifier). The data reliability and quality monitoring processes used by the PHIS database have been reported previously.(23, 24)

Dataset Linkage—We used probabilistic linkage to link the PHIS and NTDB records of patients in this dataset. The linkage methodology has been reported in detail.(25) Briefly, we applied Markov chain Monte Carlo-augmented probabilistic linkage to records of injured children (< 18 years old at admission) in the NTDB (N = 156,357) and PHIS (N = 104,049) databases from 2007–2010. We validated the accuracy of the linkage using identified data from a single center that submits to both databases.

The patients in the current study were < 18 years of age, had severe TBI (Emergency Department [ED] Glasgow Coma Scale [GCS] = 8), a hospital length of stay (LOS) of at least 24 hours, and non-missing disposition. The linkage method is accurate for these patients: sensitivity 88%, positive predictive value 98%, and specificity 99.99%.(25)

The published linkage between PHIS and NTDB yielded a cohort of 2,165 patients at 30 hospitals. For this analysis we restricted the cohort to the 2,122 patients at 29 hospitals with complete data for the variables of interest.

Variable Definitions—We defined TBI using the ICD-9-CM diagnosis codes reported by the CDC (Appendix Table 1).(1) We coded the presence of PTS and other “medical” diagnoses (cardiac arrest, for example) using ICD-9-CM diagnosis codes from the PHIS file. For injury-related variables (specific injury diagnoses including abuse/assault and intracranial hemorrhage types, injury mechanism, injury type, and severity scores), we used

ICD-9-CM diagnosis codes from the NTDB file. We defined hypotension using standard Pediatric Advanced Life Support criteria based on the pre-hospital and ED vital signs present in the NTDB. We defined the abuse/assault variable using any of ICD-9-CM diagnosis codes E960.0, E961-E968, 995.50, 995.54, 995.55, or 995.59 in the NTDB file. (26, 27) We categorized injury mechanism using the external cause-of-injury matrix created by the CDC and injury type using the Barell matrix.(28, 29) We calculated injury severity score (ISS) and maximum abbreviated injury scale (AIS) body region scores from ICD-9-CM diagnosis codes using ICDMAP-90 software.(30)

The primary outcome was PTS, defined *a priori* using previously validated ICD-9-CM diagnoses codes 345.x, 780.3, 780.33, or 780.39 (Appendix Table 1).(31) Further categorization of PTS by day of onset or phenotype (convulsive vs. non-convulsive) is not possible in our dataset because neither NTDB nor PHIS contain detail regarding timing of seizure onset or phenotype of seizure activity.

As a further validation step for this PTS definition, we analyzed the hospital records of 53 consecutive patients treated for severe TBI at a single participating center. We found that 13/53 (25%) had one of the validated set of ICD-9-CM diagnosis codes present. Of those, none had pre-existing seizures or epilepsy, and 11/13 (85%) had clinical and or EEG seizures during the acute hospitalization. The other 2/13 (15%) only had pre-hospital seizures. Both of those subjects had seizures beyond the impact period. Approximately half (7/13, 54%) were discharged from the hospital still taking AEDs.

We identified EEG monitoring using ICD-9-CM code 89.14 or 89.19 from either the NTDB or PHIS or the PHIS billing code for EEG (Appendix Table 1). We identified antiepileptic medication (AED) administration using billing data in PHIS. AED administration was defined as billing for pentobarbital, phenobarbital, levetiracetam, fosphenytoin, phenytoin, or valproic acid. Neuromuscular blockade use was defined as billing for atracurium, cisatracurium, pancuronium, rocuronium, or vecuronium.

Statistical Methods

Primary Analysis—Based on prior reports of PTS risk factors, *a priori* we chose age, abuse/assault injury mechanism, ED GCS, and intracranial hemorrhage type as candidate predictors of PTS.(5, 9, 14, 16, 17) Additionally, based on association with seizures and potential exacerbation of secondary cerebral injury, cardiac arrest, and early hypotension were selected *a priori* as candidate predictors of PTS.(17) The primary analysis was conducted using generalized estimating equations (GEEs). Modeling the odds of PTS as a multivariable function, GEEs provided robust standard errors while accounting for clustering within each hospital. We tested for effect modification by adding multiplicative interaction terms for each of the identified predictors to the multivariable model. We used standard linear regression to test the relationship between hospital severe TBI volume and hospital PTS rate.

EEG Monitoring—Because EEG monitoring use can affect PTS recognition, we conducted a secondary analysis of the relationship between PTS diagnosis and EEG monitoring in our cohort. Our data source does not distinguish prophylactic from reactive

EEG monitoring. Therefore, we are unable to explore the relationship between the time of EEG monitoring and the time of PTS diagnosis. However, we assumed 1) a singular underlying mean proportion of patients who had PTS and 2) that within each hospital the rate of PTS diagnosis would increase with increasing proportion of EEG monitoring up to a rate of EEG monitoring at which the proportion of patients with a PTS would be constant (i.e., all cases would have been found). We modeled this scenario with a piecewise log-linear regression model and weighted each hospital's influence in the model by the number of cases treated, yielding an estimate of the average proportion of patients with a PTS diagnosis and EEG monitoring use beyond which the PTS diagnosis rate is static. Location of the knot was determined by fitting many models with possible knots on a fine grid and selecting the model with the largest relative likelihood. This is equivalent to minimizing the Akaike Information Criterion (AIC).

Sensitivity Analyses—To assess the robustness of our findings, we performed sensitivity analyses to evaluate the impact of penetrating trauma on PTS rates and to compare PTS occurrence and mortality when excluding patients with LOS < 24 hours versus < 48 hours.

Software and Statistical Significance—Data analysis was conducted in R version 3.3.0.(32) GEE models were fitted using *geepack*.(33) We defined statistical significance as $P < 0.05$. Code to generate the analysis and the manuscript was written using *rmarkdown*.(34), compiled using *knitr*.(35), and is entirely reproducible.

Regulatory Approvals

This study was approved by the university institutional review board and written permission was obtained from both the Children's Hospital Association (PHIS owner) and the American College of Surgeons (NTDB owner).

Results

Hospital Characteristics and Volume

Study subjects were cared for at 29 U.S. children's hospitals. Of these, 17 (58.6%) had a American College of Surgeons (ACS) Level 1 Pediatric Trauma Center designation, 2 (6.9%) had a Level 2 designation, and the remaining 10 (34.5%) had no ACS pediatric trauma designation. Patient volume at each hospital over the four-year study period ranged from 10 to 217 total subjects, with a median (IQR) of 17.0 (9.8, 28.0) cases per hospital per year.

Patient Characteristics and Seizure Rates

Selected patient characteristics are shown in Table 1. As expected, abuse/assault as the injury mechanism was concentrated in younger children (Appendix Figure 1). PTS were diagnosed in 534 (25.2%) of the 2,122 children treated for severe TBI. Of those with seizures, most 437/534 (81.8%) were coded using the generic ICD-9-CM diagnosis code 780.39, "other convulsions." Epilepsy codes (ICD-9-CM 345.x) were present in 92/534 (17.2%) and only 5/534 (0.9%) had ICD-9-CM 780.33, "post-traumatic seizures." (780.3, convulsions, was not observed). We found no statistically significant relationship between

PTS diagnosis and hospital case volume. Children diagnosed with PTS were 3.3 years younger, on average, than those not diagnosed with PTS. Dichotomously, PTS were observed in 47.7% of children under 24 months old compared to 18.5% of those at least 24 months old (Table 2). Similarly, PTS were diagnosed in 51.1% of children injured by abuse/assault, but only 21.4% of those injured by other mechanisms. Finally, PTS were observed in 36.3% of children with SDH, compared to 21.8% of those without SDH.

With the triad of young age, injury by abuse/assault, and presence of SDH, the observed PTS rate was 57.3%. In comparison, for accidental severe TBI not including a SDH, PTS was diagnosed in 36.6% of those < 2 years old and 16.4% of those 14–17 years old. Further details of PTS occurrence and the distributions of age, injury by abuse/assault, and presence of SDH are shown in Appendix Figure 2. Injury severity measures were similar between children with and without PTS. Pre-hospital GCS (when present) was also similar between children with and without PTS (data not shown).

Hospital Course and EEG Monitoring

Hospital course information is shown in Table 3. AEDs were prescribed for over half of the cohort, and nearly twice as frequently for children with versus without PTS. EEG monitoring was ordered for just under one-third of the study population and nearly 2.5 times more frequently for children with versus without PTS. The median ICU LOS was 2 days longer (6 versus 4 days, $P < 0.01$) and the median hospital LOS was 5 days longer (12 versus 7 days, $P < 0.01$) in children with PTS versus those without. Discharge disposition was similar by PTS status. Surprisingly, PTS was associated with lower odds of death: the odds of mortality were 1.50 (95% CI: 1.10, 2.03) times greater for children without PTS compared to those with PTS.

Multivariable Analysis of Seizure Risk

Univariable and multivariable GEE results estimating the odds of PTS are shown in Table 4. In the univariable analysis, younger age, injury by abuse/assault, and SDH were factors related to higher odds of PTS. Multivariable analysis confirmed younger age, injury by abuse/assault, and presence of SDH as risk factors of PTS. For example, holding age constant, the estimated odds of PTS increased 2.6 (1.7, 3.9) fold when injury was by abuse/assault and SDH was not present. Similarly, holding age constant, when injury was not due to abuse/assault, the estimated odds of PTS increased 2.2 (1.5, 3.2) fold with SDH versus no SDH. An infant with accidental TBI and SDH has approximately the same estimated probability of PTS as an abused infant without SDH, 47% (95% CI: 39%, 55%) versus 50% (95% CI: 41%, 58%), $P = 0.69$. The triad of young age, injury by abuse/assault, and SDH confers the greatest estimated probability for PTS, 60% (95% CI: 53%, 66%).

The relationship between the risk of PTS and age is illustrated in Figure 1. The estimated odds of PTS decrease with advancing age overall, OR = 0.89 (95% CI: 0.86, 0.91) per additional year of age. While the regression results suggest that the effect modifiers age-by-abuse/assault and age-by-SDH are not statistically significant, over the range of observed data, the effects of these interactions are apparent (Figure 1). Younger children are at greater risk of PTS than older children overall. Among younger children the greatest estimated

probability of PTS is observed when both abuse/assault and SDH are present. However, the estimated difference in the probability of PTS between younger and older children differs by abuse/assault and SDH status. Estimates of the decrease in estimated PTS probability as a function of increasing age given varying abuse/assault status and SDH status are shown in Appendix Table 2.

Seizures and EEG monitoring

Figure 2 shows the proportion of patients with an ordered EEG and the proportion of patients diagnosed with PTS at each hospital. Nearly all of the hospitals with at least 20 cases reported a proportion of PTS within two standard deviations (SD) of the total cohort mean. EEG monitoring occurred, compared to PTS, with more variability between hospitals. One hospital had a higher proportion of EEG monitoring than expected (> 3 SD above the mean), but otherwise the proportion of patients with EEG monitoring at each hospital was within three SD of the total cohort mean.

We found a break-point in the piecewise linear model suggesting that the proportion of patients diagnosed with PTS was constant, 0.25 (95% CI: 0.22, 0.29), once the proportion of patients with an EEG was at least 0.25 (Figure 2). When the proportion of patients with an EEG was below 0.25, the proportion of patients diagnosed with PTS increased by a factor of 1.02 (95% CI: 1.00, 1.05) for every 1 percentage point increase in EEG monitoring.

Sensitivity Analyses

We did not exclude children with injuries that included penetrating trauma from the overall cohort. Because penetrating cranial trauma is associated with seizures(36), in a sensitivity analysis we excluded the 23/2,122 (1.1%) children with any penetrating injury as defined by the CDC external cause of injury matrix.(28) The overall PTS rate was nearly the same, 532/2,099 (25.3%) without penetrating trauma versus 534/2,122 (25.2%) including penetrating trauma.

In the overall cohort we excluded patients with a length of stay < 24 hours. To test the effect of deaths that occurred between 24 and 48 hours on the observed PTS rate, in a second sensitivity analysis we excluded the 152/2,122 (7.2%) patients who had hospital length of stay between 24 and 48 hours. The PTS rate in the remaining 1,970 patients was 516/1,970 (26.2%), only marginally different than the overall cohort rate of 534/2,122 (25.2%). Mortality in the remaining 1,970 patients was 252/1,970 (12.8%) with 54/516 (10.5%) in those with PTS. That rate is similar to the overall cohort rate of 61/534 (11.4%).

Discussion

PTS are a common complication of severe pediatric TBI. Rates of PTS range from 16.4% (14–17 years old) to 36.6% (< 2 years old) among children with accidental severe TBI not including SDH. With the triad of young age, injury by abuse/assault, and presence of SDH, the PTS rate increases to 57.3%. The estimated odds of PTS increase 2.6-fold when TBI is due to abuse/assault without SDH and increase 2.2-fold when SDH is present without abuse/assault. In contrast, the estimated odds of PTS decrease per additional year of age, OR = 0.93, when abuse/assault and SDH are not present. The interactions between age, abuse/

assault, and SDH seem to have clinically meaningful affects, such that the largest difference in risk of PTS between younger and older children is expected when both abuse/assault and SDH are present. These observed differences in estimated PTS risk suggest that it may be beneficial to tailor approaches to AED prophylaxis and EEG monitoring in children with severe TBI based on their age and the presence of SDH and/or abuse/assault.

Our study of PTS was based on the largest sample of children with TBI analyzed to date: 2,122 children treated for severe TBI at 29 hospitals. The incidence of PTS identified in our study, 25.2%, is similar to prior reports of 19–39% among pediatric study populations or subgroups restricted to severe TBI.(9, 14–16) We confirm the most commonly reported risk factors for PTS: young age(5, 9, 12, 14, 16, 17), abusive mechanism(12, 14, 17), and presence of SDH.(5, 12, 14, 17) We also corroborate reports that abusive mechanism and SDH are frequently present simultaneously, particularly in young children.(6, 18) Finally, we have identified that interactions between the risk factors of age, abuse, and SDH, while not statistically significant, appear to be clinically meaningful. We have also shown in a contemporary US dataset that the risk difference for PTS between younger and older children differs by abuse/assault and SDH status.

Other factors less consistently associated with PTS include EDH.(17) In our large sample, EDH was not associated with seizure risk. Specific skull and cerebral imaging findings, such as depressed skull fracture, intraparenchymal hemorrhage, and cerebral edema, have been associated with PTS after pediatric TBI.(4, 16) Unfortunately, our dataset does not allow assessment of these specific imaging findings.

Several diagnostic and therapeutic factors may affect diagnosis of PTS, including AED treatment and EEG monitoring.(3, 4) In our study, these factors were at the discretion of the treatment team. EEG monitoring was utilized for only 61.4% of children with PTS and 22.5% of those without PTS. Non-convulsive PTS are reported in 16–57% of children with TBI.(12, 13)

Our exploratory analysis supports additional EEG monitoring to improve PTS detection. We estimated increasing PTS recognition with increasing EEG monitoring rates up to an EEG monitoring threshold rate of 25.4%. Interestingly, this threshold rate is similar to the 28.2% of our study population diagnosed with abuse/assault, SDH, or both, as well as the 32.3% that received EEG monitoring. Our findings should be interpreted cautiously and not used to define an ideal EEG monitoring rate. Rather, our analysis corroborates that EEG monitoring may be useful to optimize PTS detection but suggests that perhaps a threshold exists beyond which additional EEG monitoring does not capture additional PTS. Further prospective investigation is needed to determine the optimal EEG monitoring practices for children with severe TBI.

PTS have consistently been associated with worse functional outcomes after pediatric TBI. (5, 7–9, 37) In our study, PICU and hospital LOS were longer among children with PTS. However, a diagnosis of PTS was unexpectedly associated with lower mortality. A sensitivity analysis confirmed that early deaths did not bias this comparison. This finding is surprising and deserves further exploration. Varying study design, heterogeneity of study

populations and/or incomplete recognition of PTS may contribute to differences between our study and prior reports. Our study population was limited to children with severe TBI who survived at least 24 hours after injury. Prior reports have not clearly excluded early deaths and/or have included wider variability of TBI severity (i.e. both moderate and severe TBI). (5, 8, 9) One may speculate that in our population, earlier mortality may have been associated with insufficient time to exhibit seizure activity. However, a sensitivity analysis that excluded children who failed to survive for at least 48 hours corroborated our initial findings of lower mortality among those with versus without PTS. Further, the strongest associations between PTS and poor outcome are identified among investigations limited to children with TBI due to abuse/assault.(6, 37) Although our study includes 270 children with TBI due to abuse/assault, this comprises only 12.7% of the total sample. Finally, we were unable to classify seizures by time of occurrence. Impact seizures, which occur immediately after TBI, are not associated with worse outcomes. The validation study we performed suggests that we did not capture impact seizures. The unexpected finding of an inverse association between PTS and mortality could generate a hypothesis that the brain can be “too injured to seize” or lend support to speculation that PTS may have an adaptive component that helps counteract post-TBI neuronal depression.(38) Additional pre-clinical and clinical studies are warranted.

Strengths of our study include generalizability, as this is the first pediatric PTS investigation to utilize two national multi-center databases, the NTDB and PHIS. Limitations to our study not mentioned previously include those inherent to the retrospective observational design. The population in this study was more heterogeneous than other published studies of children with severe TBI, as we did not exclude young infants(39, 40), patients with known or suspected child abuse(39–42), patients with isolated acute epidural hematoma(39, 40), or patients without abnormalities on the first CT scan(39, 40, 42). The median ICU length of stay that we found, 4 days, was longer than that reported in a single-center retrospective cohort study (2 days)(41) but shorter than investigators observed in a multi-center efficacy trial (11 days) with a more homogeneous study population and a temperature-control protocol that could lengthen the ICU stay.(39)

We defined PTS using a set of diagnosis codes for seizures that were validated previously in a different population.(31) We confirmed that those codes identify PTS in a small sample of children with severe TBI from one institution. This validation step suggests that these codes do not capture impact seizures, but may capture a few children who only had seizures during the pre-hospital phase of care. The 12.0% of children in our study who seized and did not receive AEDs may have only had PTS before arriving at the hospital. Because benzodiazepines are frequently used as sedatives in children with severe TBI, we did not include benzodiazepine use in the AED definition in this study. Children who received only a benzodiazepine for a brief PTS might also be among the 12.0% patients diagnosed with PTS who did not receive longer-acting AEDs.

Most 437/534 (81.8%) of the patients diagnosed with seizures in our study were coded using a generic “other convulsions” diagnosis code (ICD-9-CM 780.39). The specific diagnosis code for post-traumatic seizures, 780.33, went into service on October 1, 2010(43), near the end of our cohort. It was present in the records of only a few subjects in our study.

Determining whether or not 780.33 gets used more often for patients with TBI in the future will require further study.

Diagnostic and therapeutic interventions were determined by procedure codes and billing data. Classification of TBI characteristics was limited to diagnosis codes and trauma registry fields, limiting assessment of specific injury characteristics. Hypoxia is another potential predictor of seizures. We did not have a reliable variable for hypoxia in our dataset. The pre-hospital and ED vital signs in the NTDB include oxygen saturation, but that variable had too much missing data, 84.0%, to include in our analysis. The rate of hypotension we found, 221 (10.4%), is lower than expected based on previous reports with hypotension rates close to 40%. (44) Unfortunately, approximately one-third of children with TBI don't have either blood pressure or oxygen saturation measured during the pre-hospital or ED phases of care. (44) Lack of measurement likely contributed to the missing data regarding oxygen saturation. Finally, TBI severity was determined by ED GCS, which may be influenced by administration of sedative and/or neuromuscular blocking agents and can overestimate TBI severity.

In conclusion, PTS are a common complication of severe pediatric TBI. Younger age, injury by abuse/assault, and SDH are early predictors for PTS; however, PTS remain common even in the absence of these factors. Additionally, interactions between these risk factors, although not statistically significant, appear to be clinically meaningful. Additional investigations are needed to further delineate interactions between age, abusive mechanism, and SDH, to explore the influence of EEG monitoring on PTS diagnosis, and to better describe care utilization patterns of AED prophylaxis and EEG monitoring for children with severe TBI.

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Appendix

Appendix Figure 1. Injury Mechanism by Age

“E Code” = ICD-9-CM diagnosis E code. MV = Motor Vehicle crash.

Appendix Figure 2. Seizure Frequency by Injury Mechanism and Subdural Hematoma status

PTS = Post-traumatic seizure. SDH = Subdural hematoma

Appendix Table 1

Database Codes for Diagnoses and Procedures

	PHIS ICD-9-CM codes		NTDB ICD-9-CM codes		CTC codes
Diagnosis/Procedure					
TBI	800.0–801.9, 803.0–804.9, 850–854.1, or 959.01 ¹	AND	800.0–801.9, 803.0–804.9, 850–854.1, or 959.01		
Seizure	345.x, 780.3, 780.33, or 780.39 ³¹				
Cardiac arrest	427.5x				
Abuse/Assault			E960.0, E961–E968, 995.50, 995.54, 995.55, or 995.59 ^{26,27}		
EDH [*]			852.4x – 852.5x		
SAH [*]			852.0x – 852.1x		
SDH [*]			852.2x – 852.3x		
EEG	89.14 or 89.19	OR	89.14 or 89.19	OR	515001

* All without skull fracture. PHIS = Pediatric Health Information Systems. ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification. NTDB = National Trauma Data Bank. CTC = Clinical Transaction Classification. TBI = Traumatic Brain Injury. EDH = Epidural hematoma. SAH = Subarachnoid hemorrhage. SDH = Subdural hematoma.

Appendix Table 2

Interactions of Age, Abuse/Assault, and SDH relative to Seizure Risk

	OR per additional month (95% CI)	OR per additional year (95% CI)
Abuse/Assault, SDH	0.984 (0.974, 0.993)	0.820 (0.730, 0.922)
No Abuse/Assault, SDH	0.986 (0.981, 0.992)	0.849 (0.792, 0.911)
Abuse/Assault, No SDH	0.991 (0.981, 1.001)	0.897 (0.794, 1.014)
No Abuse/Assault, No SDH	0.994 (0.992, 0.996)	0.929 (0.905, 0.954)

OR = Odds ratio. CI = Confidence interval. SDH = Subdural hematoma.

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Figure 1. Seizure Probability by Age, Abuse, SDH, and their interactions

Estimated Seizure Probability with 95% confidence bands. Confidence band for Abuse/Assault = "Yes" and SDH = "No" not shown to improve readability. SDH = Subdural hematoma.

Figure 2. Proportion of patients with Seizure and EEG

Piecewise linear model shown with 95% confidence bands. EEG = electroencephalogram.

Limited to hospitals with > 20 patients overall.

Table 1**Patient and Injury Characteristics**

	All: n = 2,122	No Seizure: 1,588 (74.8%)	Seizure: 534 (25.2%)
Age, years			
mean ± SD	7.5 ± 5.5	8.4 ± 5.3	5.0 ± 5.3
Male			
n (%)	1,325/2,115 (62.6)	993/1,582 (62.8)	332/533 (62.3)
Admit Year			
2007: n (%)	314 (15)	233 (15)	81 (15)
2008: n (%)	667 (31)	492 (31)	175 (33)
2009: n (%)	578 (27)	440 (28)	138 (26)
2010: n (%)	563 (27)	423 (27)	140 (26)
Injury Mechanism			
Abuse/Assault: n (%)	270 (13)	132 (8)	138 (26)
Fall: n (%)	317 (15)	218 (14)	99 (19)
Motor Vehicle: n (%)	906 (43)	769 (48)	137 (26)
Other: n (%)	628 (30)	468 (29)	160 (30)
No E Code: n (%)	1 (0)	1 (0)	0 (0)
Hemorrhage Type^f			
EDH: n (%)	104 (5)	86 (5)	18 (3)
SAH: n (%)	324 (15)	236 (15)	88 (16)
SDH: n (%)	496 (23)	316 (20)	180 (34)
Mechanism/Hemorrhage Combination			
No Abuse/Assault, No SDH: n (%)	1,524 (72)	1,216 (77)	308 (58)
Abuse/Assault, No SDH: n (%)	102 (5)	56 (4)	46 (9)
No Abuse/Assault, SDH: n (%)	328 (15)	240 (15)	88 (16)
Abuse/Assault and SDH: n (%)	168 (8)	76 (5)	92 (17)
Cardiac Arrest			
n (%)	72 (3)	51 (3)	21 (4)
Hypotension			
n (%)	221 (10)	171 (11)	50 (9)
Head AIS			
Minor: n (%)	20 (1)	14 (1)	6 (1)
Moderate: n (%)	223 (11)	171 (11)	52 (10)
Serious: n (%)	666 (32)	521 (34)	145 (28)
Severe: n (%)	788 (38)	570 (37)	218 (42)
Critical: n (%)	364 (18)	268 (17)	96 (19)
Missing: n (%)	61 (3)	44 (3)	17 (3)
ISS			
< 15: n (%)	695 (33)	510 (32)	185 (35)
15: n (%)	1,427 (67)	1,078 (68)	349 (65)
GCS			

	All: n = 2,122	No Seizure: 1,588 (74.8%)	Seizure: 534 (25.2%)
3–5: n (%)	1,519 (72)	1,143 (72)	376 (70)
6–8: n (%)	603 (28)	445 (28)	158 (30)

¹ All without skull fracture. Due to rounding, percentages in each group may not add to 100. EDH = Epidural hematoma. SAH = Subarachnoid hemorrhage. SDH = Subdural hematoma. AIS = Maximum Head Abbreviated Injury Scale score. ISS = Injury Severity Score, derived using ICDMAP-90 software.

Table 2

Seizures and Seizure Risk Factors by Age

	Age < 2 year: n = 486 (22.9%)	Age ≥ 2 year: n = 1,636 (77.1%)	p-value
Seizure, n (%)	232 (48)	302 (18)	$P < 0.01$
Abuse/Assault, n (%)	199 (41)	71 (4)	$P < 0.01$
SDH, n (%)	232 (48)	264 (16)	$P < 0.01$
No Abuse, No SDH, n (%)	186 (38)	1,338 (82)	$P < 0.01$
No Abuse, SDH, n (%)	101 (21)	227 (14)	$P < 0.01$
Abuse, No SDH, n (%)	68 (14)	34 (2)	$P < 0.01$
Abuse, SDH, n (%)	131 (27)	37 (2)	$P < 0.01$

SDH = Subdural hematoma. "Abuse" = Abuse/Assault. P-values from GEE models of the odds of the listed risk factor by age.

Table 3**Hospital Course**

	All: n = 2,122	No Seizure: 1,588 (74.8%)	Seizure: 534 (25.2%)
Medications and Monitoring			
AED, n (%)	1,198 (56)	728 (46)	470 (88)
NMB, n (%)	1,376 (65)	996 (63)	380 (71)
EEG, n (%)	685 (32)	357 (22)	328 (61)
ICU Admission			
Admitted to ICU, n (%)	2,030 (96)	1,507 (95)	523 (98)
Lengths of Stay			
ICU (days), median(IQR)	4 (2, 10)	4 (2, 10)	6 (2, 13)
Hospital (days), median(IQR)	8 (3, 20)	7 (3, 18)	12 (4, 25)
Hospital Disposition			
Home with Services: n (%)	46 (2)	29 (2)	17 (3)
Home without Services: n (%)	1,139 (54)	849 (53)	290 (54)
Transfer to Care Facility: n (%)	219 (10)	154 (10)	65 (12)
Transfer to Rehab: n (%)	397 (19)	298 (19)	99 (19)
Mortality: n (%)	318 (15)	257 (16)	61 (11)
Other: n (%)	3 (0)	1 (0)	2 (0)

Percentages are by column for each group. AED = Antiepileptic Drug. NMB = Neuromuscular Blockade. EEG = Electroencephalogram. ICU = Intensive Care Unit. IQR = Interquartile range. "Rehab" = Inpatient Rehabilitation.

Table 4

Generalized Estimating Equations Models for Seizure

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age		
Per additional month	0.990 (0.988, 0.992)	0.994 (0.992, 0.996)
Per additional year	0.89 (0.86, 0.91)	0.93 (0.90, 0.95)
Abuse/Assault		
Abuse/Assault vs No Abuse/Assault	3.9 (2.9, 5.3)	2.6 (1.7, 3.9)
Cardiac Arrest		
Cardiac Arrest vs No Cardiac Arrest	1.2 (0.8, 2.0)	0.7 (0.4, 1.4)
Hypotension		
Hypotensive vs Not Hypotensive	0.87 (0.71, 1.05)	0.8 (0.6, 1.0)
ED Glasgow Coma Scale		
ED GCS 6–8 vs 3–5	1.10 (0.84, 1.43)	1.10 (0.83, 1.46)
Hemorrhage Type[/]		
EDH vs No EDH	0.6 (0.4, 1.0)	0.7 (0.4, 1.1)
SAH vs No SAH	1.11 (0.87, 1.43)	0.8 (0.6, 1.1)
SDH vs No SDH	2.1 (1.7, 2.6)	2.2 (1.5, 3.2)
Effect Modifiers		
Abuse/Assault by SDH		0.7 (0.4, 1.1)
Age (years) by Abuse/Assault		0.97 (0.86, 1.08)
Age (years) by SDH		0.91 (0.85, 0.98)

OR = Odds ratio. CI = Confidence interval. ED = Emergency Department. GCS = Glasgow Coma Scale.

[/] All without skull fracture. EDH = Epidural hematoma. SAH = Subarachnoid hemorrhage. SDH = Subdural hematoma.