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ORIGINAL ARTICLE

Early post-traumatic seizures in hospitalized patients with traumatic brain injury

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Objectives: Early post-traumatic seizures (EPTS) are a well-known complication of traumatic brain injury (TBI). EPTS increase the risk of secondary brain injury and may cause significant challenges during the period of critical care. Routine use of prophylactic anti-seizure medication is controversial due to conflicting reports on efficacy and risk of adverse effects. The purpose of this study was to expand the understanding of EPTS by examining incidence and risk factors in hospitalized patients with TBI.

Material & Methods: Adult patients with TBI and evidence of intracranial injury admitted to Oslo University Hospital between 2015 and 2019 were identified from the Oslo TBI Registry - Neurosurgery. Demographic and clinical data including occurrence of seizures were retrieved from the registry. The patients did not receive routine seizure prophylaxis. Univariate and multivariable logistic regression analyses were used to investigate risk factors associated with EPTS.

Results: 103 of 1827 patients (5.6%) had new-onset seizures within the first week after TBI. The following factors were in multivariable analyses associated with EPTS; alcohol abuse (odds ratio [OR] 3.6, 95% CI 2.3–5.7, $p < .001$), moderate and severe brain injury (OR 2.2, 95% CI 1.3–3.8, $p = .004$ and OR 2.1, 95% CI 1.2–3.6, $p = .012$), brain contusion (OR 1.6, 95% CI 1.0–2.4, $p = .046$) and subdural hematoma (OR 1.6, 95% CI 1.0–2.6, $p = .052$).

Conclusion: In our material, EPTS occurred in 5.6% of hospital-admitted TBI-patients. Alcohol abuse was the most significant risk factor, followed by moderate and severe brain injury. The results of this study contribute to the discussion about preventive treatment of EPTS in certain risk groups.

KEYWORDS
alcohol abuse, brain contusion, early post-traumatic seizures, epilepsy, prophylaxis, subdural hematoma, traumatic brain injury

Hild Flatmark Sødal and Gøril Storvig have contributed equally to this work and should be considered joint first author

1 | INTRODUCTION

Traumatic brain injury (TBI) is a major health problem and can have a decisive impact on functional capacity and quality of life.[1,2] Epileptic seizures are a common complicatio that adds an additional burden to the challenges of TBI.[3,4] Onset of post-traumatic seizures varies from seconds to several years after brain injury. Early post-traumatic seizures (EPTS) are usually defined as seizures occurring within the first 7 days after injury. They are categorized as acute symptomatic seizures, as they do not carry a high risk of future seizures.[5] Late post-traumatic seizures, which occur more than 1 week after brain injury, indicate an ongoing process of epileptogenesis and constitute the diagnosis of post-traumatic epilepsy (PTE).[6] EPTS are associated with an increased risk of PTE,[7,8] but it is still unclear what role they represent in the process of epileptogenesis.

The incidence of EPTS ranges from 0.4% to 26.7%, depending on study population and methods for seizure detection.[9–12] They are associated with increased intracranial pressure, worsening cerebral edema, and metabolic crisis.[13,14] This may cause significant challenges during the period of critical care and result in worse outcomes, including longer hospital stay and poorer functional outcome over time.[9,10,15] Anti-seizure medication (ASM) given early after TBI reduces the incidence of EPTS but has not been effective in preventing development of PTE.[16,17] Guidelines from the American Academy of Neurology and the Brain Trauma Foundation recommend that seizure prophylaxis with phenytoin should be used during the first week after severe TBI.[18,19] This remains controversial because of conflicting reports about the efficacy and adverse effects associated with such treatment.[20] Consequently, the use of seizure prophylaxis after TBI is not routine in many countries, including Norway. Use of levetiracetam for preventing and treating epileptic seizures is increasing. Levetiracetam is better-tolerated and possesses similar efficacy in preventing epileptic seizures,[21,22] and it may even have anti-epileptogenic effects.[23] Identifying and treating patients at high risk of EPTS may prevent further brain damage, reduce hospital stay, and possibly be beneficial in preventing the development of PTE.

The aim of this study was to investigate the incidence and potential risk factors for EPTS in hospital-admitted TBI patients in order to discuss the potential benefit of routine use of seizure prophylaxis.

2 | MATERIALS & METHODS

2.1 | Participants and data collection

We conducted an observational cohort study based on data extracted from the Oslo TBI Registry – Neurosurgery at Oslo University Hospital (OUH), Norway.[24] OUH is the only trauma center with neurosurgical services in the Southeast region of Norway, covering a population of 3 million. The inclusion criteria for the TBI Registry are neuroimaging findings of acute trauma, admission at OUH within 7 days after TBI, and having a Norwegian social security number. Data are collected from medical records by dedicated health care professionals at the department of Neurosurgery at OUH.

In the present study, we included all patients ≥18 years of age with TBI in the period January 1, 2015–December 31, 2019. Excluded were subjects with a history of seizures prior to TBI, including diagnosis of epilepsy. Variables extracted from the database included demographic data, comorbidity, injury mechanism and severity, neuroimaging findings, seizures occurring within the first week after TBI, length of acute admission (intensive care unit [ICU] and/or neurosurgical care), and date of death. The patients did not receive routine seizure prophylaxis.

Preinjury health status was classified according to American Society of Anesthesiologists (ASA) Physical Status Classification System (ASA score 1–6; where 1 is a healthy patient and 6 is a declared brain-dead patient)[25]. Alcohol- and substance abuse was registered if explicitly stated in the medical journal. High-energy trauma was defined as incidents involving motorized vehicles, bikes, skiing at high speed, crushing injuries, and falls from a height ≥3 meters. Brain injury severity was defined using the Head Injury Severity Scale (HISS) where *Minimal* refers to Glasgow Coma Scale (GCS) 15 and no loss of consciousness (LOC) or amnesia, *Mild*: GCS 14–15, LOC <5 min or impaired memory or reactiveness, *Moderate*: GCS 9–13, LOC ≥5 min or focal neurological deficits and *Severe*: GCS 3–8.[26]

The neuroradiological findings were based on the first computed tomography (CT) scan upon arrival at OUH and were divided into the following categories: subdural hematoma, epidural hematoma, subarachnoid hemorrhage, brain contusion (including intracerebral hematoma), intraventricular hemorrhage, penetrating head injury, depressed skull fracture, and other skull fractures. Information on size, number, and anatomical localization of hemorrhages was not available. Appearance of diffuse axonal injury (DAI) was in all cases verified with magnetic resonance imaging (MRI).

The primary outcome variable was EPTS, defined as at least one seizure observed or described by health care professionals within the first 7 days after TBI. It was specified whether seizures were immediate (occurring within the first 24 h) or early (occurring from day 1 to day 7), or both.

The study was approved as a quality control study by the Data Protection Officer at OUH (19/02587).

2.2 | Statistical methods

Descriptive statistics are presented as means with standard deviations, medians with ranges, and frequencies with percentages when appropriate. Differences between the seizure group and the non-seizure group were investigated using *t*-test for continuous variables and Chi-square test for categorical variables. Logistic regression analyses were conducted to investigate the associations between potential risk factors and EPTS. Variables with a significance value <0.1 in the univariate analyses were entered into a multivariable logistic regression model. Using a stepwise backward elimination strategy, all the remaining risk factors in the final model had a

significance level ≤0.05. Age and sex were re-entered into the model to investigate their influence on the remaining risk factors. Odds ratio (OR) and the corresponding 95% CI were reported. In the logistic regression analyses, the ASA score was dichotomized into ASA ≤2 (patients with no or mild systemic disease) and ASA ≥3 (patients with severe systemic disease). Minimal and mild brain injuries were merged into one category, leaving three categories (Minimal & mild, Moderate, and Severe). For all injury-specific variables, the category with lowest severity was used as the reference. A significance level of 0.05 was applied where not stated otherwise. All statistical analyses were conducted using IBM SPSS Statistics version 26.0.

3 | RESULTS

1917 patients ≥18 years old with CT-verified TBI were admitted at OUH during the study period. Of these, 90 had a history of seizures prior to TBI and were excluded. The remaining 1827 patients were defined as the study participants and included in the statistical analyses.

The demographic and clinical characteristics of the participants are presented in Table 1. The mean patient age was 57 years (SD 21, range 18–98), 69% were males, 30% had major preinjury comorbidity (ASA scores ≥3), and 55% had moderate-to-severe TBI.

Of the study participants, 103 (5.6%) developed EPTS. Of these, 63 had immediate seizures, accounting for 61% of all EPTS. Patients with EPTS compared to patients without EPTS had a significant higher mean age, higher ASA score, a higher percentage of alcohol abuse, less high-energy trauma, higher percentage of moderate and severe brain injuries, and more often subdural hematoma and brain contusion (Table 1). There were no significant differences between the groups with respect to sex, substance abuse, frequencies of skull fracture, epidural hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage. Because of few observations of penetrating injury and depressed skull fracture, these variables were excluded from the analyses.

An MRI scan was performed in 456 (25%) of the participants, more often in the group with EPTS (34 vs. 24%, $p = .039$). In 10 subjects, MRI could not determine if DAI was present or not. 250 (56%) of the remaining patients had evidence of DAI. There was no significant difference in the occurrence of EPTS in patients with DAI compared to the patients without DAI $p = .204$). DAI was not included in further analyses.

EPTS patients compared to patients without EPTS had longer acute hospital stay (median length 7 vs. 4 days, $p < .001$). There was no difference in in-hospital mortality between the groups (8 vs. 9%, $p = .915$).

TABLE 1 Demographics, preinjury conditions, and injury characteristics among patients with and without early post-traumatic seizures (EPTS)

	All *n* = 1827	EPTS *n* = 103	No EPTS *n* = 1724	*p*-value
Age, years (mean, SD)	57 (21)	61 (17)	57 (21)	**.041**
Sex, male, *n* (%)	1253 (69)	77 (75)	1176 (68)	.200
Preinjury ASA score, *n* (%)				**<.001**
ASA 1	739 (40)	25 (24)	714 (41)	
ASA 2	527 (29)	31 (30)	496 (29)	
ASA 3	538 (29)	42 (41)	496 (29)	
ASA 4	23 (1)	5 (5)	18 (1)	
Alcohol abuse, *n* (%)	220 (12)	34 (33)	186 (11)	**<.001**
Substance abuse, *n* (%)	119 (7)	7 (7)	112 (7)	1.000
HISS, *n* (%)				**<.001**
Minimal	105 (6)	1 (1)	104 (6)	
Mild	730 (40)	23 (22)	707 (41)	
Moderate	527 (29)	43 (42)	484 (28)	
Severe	465 (26)	36 (35)	429 (25)	
High-energy trauma, *n* (%)†	662 (37)	18 (19)	644 (38)	**<.001**
Penetrating head injury, *n* (%)	38 (2)	1 (1)	37 (2)	N/A
Skull fracture, *n* (%)	906 (50)	50 (49)	856 (50)	.907
Depressed skull fracture, *n* (%)	90 (5)	5 (5)	85 (5)	N/A
Epidural hematoma, *n* (%)	248 (14)	15 (15)	233 (14)	.878
Subarachnoid hemorrhage, *n* (%)	1122 (61)	72 (70)	1050 (61)	.086
Subdural hematoma, *n* (%)	1059 (58)	77 (75)	982 (57)	**<.001**
Intraventricular hemorrhage, *n* (%)	228 (13)	14 (14)	214 (12)	.843
Brain contusion, *n* (%)	899 (49)	65 (63)	834 (48)	**.005**

Abbreviations: ASA, American Society of Anesthesiologists Physical Status Classification System; HISS, Head Injury Severity Scale; N/A, not applicable; SD, standard deviation

Significant values are presented in bold

†The presented % are based on non-missing data only ($n = 1783$).

3.1 | Risk factors associated with EPTS

The following factors were in the univariate regression analyses significantly associated with an increased probability of EPTS: age between 60–74 years, ASA score ≥3, alcohol abuse, moderate and severe brain injury, subdural hematoma, and brain contusion (Table 2). High-energy trauma was associated with decreased probability of EPTS.

Variables with significant or near significant associations ($p < .1$) assumed to be risk factors for EPTS were further investigated in a

multivariable logistic regression model. The variable "high-energy trauma" was not included in the model.

In the multivariable logistic regression analysis, alcohol abuse was the most robust risk factor associated with EPTS (OR 3.6, 95% CI 2.3–5.7, $p < .001$), followed by moderate and severe head injury (OR 2.2, 95% CI 1.3–3.8, $p = .004$ and OR 2.1, 95% CI 1.2–3.6, $p = .012$, respectively), brain contusion (OR 1.6, 95% CI 1.0–2.4, $p = .046$), and subdural hematoma (OR 1.6, 95% CI 1.0–2.6, $p = .052$). The results are presented in Table 3. All variables were adjusted for age, sex, and the other variables included in the model. When re-entering age and sex into the final model, the p-value of the association between subdural hematoma and risk of EPTS increased ($p = .031$ to $p = .052$). No significant changes were observed in the other variables.

Possible interaction effects were examined between the variables in the final model, but none was of statistical significance. Variance inflation factor (VIF) was applied to detect multicollinearity; all risk factors had VIF values ≤1.6.

4 | DISCUSSION

In this study of 1827 hospital-admitted adults with TBI, EPTS occurred in 5.6%. Alcohol abuse was the most significant risk factor associated with EPTS, followed by moderate and severe brain injury. Evidence of subdural hematoma and/or brain contusion on admission CT-scan was also associated with an increased probability of EPTS.

TABLE 2 Univariate logistic regression analyses of potential risk factors associated with early post-traumatic seizures

Variable	Unadjusted OR (95% CI)	*p*-value
Sex (male)	1.4 (0.9–2.2)	.166
Age (ref. group 18–39 years, $n = 439$)		.164
40–59 years ($n = 411$)	1.2 (0.7–2.3)	.485
60–74 years ($n = 489$)	1.8 (1.0–3.2)	**.040**
75–98 years ($n = 488$)	1.2 (0.6–2.2)	.591
Preinjury ASA score ≥3	2.0 (1.3–3.0)	**<.001**
Alcohol abuse	4.1 (2.6–6.3)	**<.001**
Substance abuse	1.1 (0.5–2.3)	.905
HISS		**<.001**
Moderate	3.0 (1.8–5.0)	**<.001**
Severe	2.8 (1.7–4.8)	**<.001**
High-energy trauma[†]	0.4 (0.2–0.6)	**<.001**
Skull fracture	1.0 (0.6–1.4)	.827
Epidural hematoma	1.1 (0.6–1.9)	.763
Subarachnoid hemorrhage	1.5 (1.0–2.3)	.070
Subdural hematoma	2.2 (1.4–3.5)	**<.001**
Intraventricular hemorrhage	1.1 (0.6–2.0)	.725
Brain contusion	1.8 (1.2–2.8)	**.004**

Abbreviations: ASA, American Society of Anesthesiologists Physical Status Classification system; CI, confidence interval; HISS, Head Injury Severity Scale; OR, odds ratio.

Significant values are presented in bold

[†]Only non-missing data were included in the analysis ($n = 1783$).

The incidence of EPTS ranges from 0.4 to 26.7% among previous studies. The large variation is related to differences in study population, applied definitions and seizure detection, and makes comparison between studies difficult. In a recent study based on a nationwide trauma database in the USA, Majidi et al. found that in-hospital seizures occurred in 0.4%.[10] In this study, diagnostic codes were used to identify TBI-patients with seizures, which could potentially lead to an underestimation of seizures. Another reason for the low incidence may be use of prophylactic anti-seizure medication. In a prospective multicenter study by Ritter and colleagues, EPTS occurred in 10.7%.[12] The high proportion of severe brain injuries among the participants compared to our cohort (90.1% vs. 26%) may explain the lower incidence in our study. In the study mentioned, a high proportion of in-hospital seizures occurred during the first 24 h after TBI (72.4%).[12] Similar findings were reported in the studies by Kollevold[27] and corresponds well with our results (61%).

The highest incidence of EPTS is shown in ICU continuous electroencephalogram (cEEG) studies. Vespa et al. reported an incidence of electrographic seizures of 22% in subjects with moderate-to-severe TBI, with 52% of the seizures being nonconvulsive.[28] A more recent study on the same population found that 26.7% of the patients had nonconvulsive or clinical seizures based on cEEG analysis.[9] We have no information about the use of EEG or cEEG in our cohort. Availability of cEEG in our center is low, indicating that seizure detection was mainly based on clinical observation.

We found that alcohol abuse is strongly associated with seizures during the first week after TBI. Alcoholism as a risk factor for post-traumatic seizures is well-described in the literature.[29,30] The increased risk of new-onset seizures in subjects with alcohol abuse may be related to several factors, including alcohol withdrawal, electrolyte imbalance, and head trauma itself. We consider the frequency of alcohol withdrawal seizures to be low in our cohort since preventive treatment with benzodiazepines is usually administered to patients at risk. Benzodiazepines will also suppress trauma-induced seizures; hence, the odds of having EPTS in patients with alcohol abuse is probably even higher than demonstrated. Information about drinking habits is often limited in the medical records, and the prevalence of alcohol abuse is often underestimated.[31] Increased attention toward alcohol abuse in subjects with TBI, including the use of blood biomarkers, could improve diagnostics and intervention to prevent seizures. Our results suggest that other patient-related variables, such as sex, age, and a preexisting moderate-to-severe disease are not independent risk factors for EPTS in the adult population.

We demonstrated that moderate and severe brain injury are independent risk factors associated with EPTS. This is in agreement with previous studies. Higher injury severity has been described as an important risk factor for both early and late post-traumatic seizures.[15,32,33] Classification of severity of TBI varies considerably, and different markers of injury probably represent different aspects of brain damage.[33] In previous studies, injury severity stratification is

TABLE 3 Multivariable model of risk factors associated with early post-traumatic seizures

Risk factor	Adjusted OR (95% CI)	*p*-value
Alcohol abuse	3.6 (2.3–5.7)	<.001
HISS		.011
Moderate	2.2 (1.3–3.8)	.004
Severe	2.1 (1.2–3.6)	.012
Brain contusion	1.6 (1.0–2.4)	.046
Subdural hematoma	1.6 (1.0–2.6)	.052

Abbreviations: CI, confidence interval; HISS, Head Injury Severity Scale; OR, odds ratio.

Variables with $p < .1$ in the univariate analyses were included in the multivariable logistic regression model and reduced using backwards elimination. The risk factors in the final model are adjusted for age, sex and the other variables in the model.

based on different combinations of parameters including GCS, neurological complications, and neuroradiological findings.[7,9,12] In our study, injury severity was categorized according to the HISS, which is widely used in the Scandinavian countries. In spite of the differences in the assessment, injury severity seems to be a robust risk factor for EPTS.

The identification of subdural hematoma and brain contusion as potential risk factors for EPTS is consistent with previous findings.[8,30,33] However, the estimated odds ratios were considerably reduced when adjusting for the other variables in the multivariable model (Table 3), resulting in 95% CIs including 1.0. *p*-values for both variables are close to 0.05, leaving a slight probability that the associations are by chance. Similar findings were made for subarachnoid hemorrhage, which did not reach significance in the multivariable model. This indicates that the association between intracranial hemorrhages and EPTS is explained by other factors such as injury severity and alcohol abuse. We found that epidural hematoma, intraventricular hemorrhage, DAI, and skull fracture (non-depressed) are not associated with EPTS, probably because of less degree of cortical irritation from blood products.[33] Even with a large sample size, the prevalence of penetrating injury and depressed skull fractures was low; hence, we were not able to investigate their association with EPTS. Previous findings suggest that these factors are associated with EPTS.[8] Surprisingly, there was significantly less high-energy trauma in subjects with EPTS (19% vs. 38%, $p < .001$). One explanation for this may be that the high-energy forces lead to more severely injured patients that are more likely to be sedated during the first week, suppressing convulsive seizures. We cannot explore this hypothesis further, as information regarding use of sedatives was not available. As a result, we decided not to include high-energy trauma in the multivariable model.

EPTS are dramatic events that can worsen secondary brain damage as a result of increased inflammatory response and cerebral metabolic distress.[34,35] This may cause significant challenges during the period of critical care. We found that patients with EPTS have significantly longer acute hospital stay compared to patients without EPTS. In a recent study by Laing et al., new-onset seizures during acute admission after TBI were associated with admission to ICU, mechanical ventilation, longer duration of mechanical ventilation, ICU care and hospital stay, and a higher probability of discharge to inpatient rehabilitation.[15] Guidelines recommend the use of prophylactic ASM to decrease the incidence of EPTS.[18,19] However, there are controversies regarding the effectiveness and risks associated with such treatment.[11,20] Considering the relatively low rates of EPTS even in hospitalized TBI-patients, one may question if routine use of anti-seizure medication to prevent EPTS is warranted for all TBI-patients with higher injury severity.

Our study documents the importance of independent risk factors that can be identified at an early stage after injury and has potential clinical implications regarding the use of ASM prophylaxis in TBI-subjects. Use of seizure prophylaxis in hospital-admitted TBI-patients with a combination of these risk factors could prevent further brain damage and reduce hospital stay in a high-risk group. As previously pointed out, most EPTS are immediate; hence, effective prophylaxis requires intravenous drug loading as soon as possible after injury. To avoid the potential harmful adverse effects and challenges of the pharmacokinetics with phenytoin, levetiracetam may be an effective and safe alternative.[36–38] Recent studies have demonstrated that early intervention with both levetiracetam and its analog brivaracetam may have the potential to interfere with the development of PTE.[39–41]

This is an observational registry-based study, and conclusions regarding the causal relationship between risk factors and EPTS cannot be drawn. The strengths of the study are the large sample size and the manual data collection by dedicated health care professionals, reducing the risk of information bias. There is a high probability that the registered seizures were related to TBI, as all subjects with previous epilepsy were excluded. The use of multivariable analysis is a strength as it displays the significance of independent risk factors. However, the possibility of classification into several injury types and the frequent co-occurrence of subdural hematoma, brain contusion, and subarachnoid hemorrhage makes it difficult to interpret their individual contribution to seizure risk.

The use of ASA score as a proxy for preinjury comorbidities that can contribute to early seizures can be beneficial in a clinical setting due to its ease of use. Nevertheless, it is not optimal as higher scores may be a result of conditions without a clear causal effect on seizures. Evaluation of specific comorbidities could be more helpful in identifying patients with a high risk of seizures. Another limitation is the low frequency of penetrating injuries and depressed skull fractures, making it difficult to evaluate these types of injury. The lack of cEEG-monitoring and thus the limited ability to detect nonconvulsive seizures has probably led to an underestimation of EPTS in our study. Furthermore, we cannot evaluate whether the identified risk factors have similar effect on nonconvulsive seizures.

5 | CONCLUSION

This study adds to the literature on EPTS and documents the significance of clinical risk factors that can be identified early after TBI.

Information about alcohol habits should be sought in TBI-subjects as we found a strong association between alcohol abuse and EPTS. Use of prophylactic anti-seizure medication in hospital-admitted TBI-patients with a combination of documented risk factors could improve patient care and outcome after TBI.

AUTHOR CONTRIBUTIONS

Conception and design: HFS, EH, and ET. Data collection: CT, HFS, and EH. Analysis and interpretation of data: HFS, GS, HSR, EH, and ET. Drafting the manuscript: HFS and GS. Critical revisions and approval of final manuscript: all authors.

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CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

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