RESEARCH ARTICLE

Association of Posttraumatic Epilepsy With Long-term Functional Outcomes in Individuals With Severe Traumatic Brain Injury

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Abstract

Background and Objective

Nearly one-third of patients with severe traumatic brain injury (TBI) develop posttraumatic epilepsy (PTE). The relationship between PTE and long-term outcomes is unknown. We tested whether, after controlling for injury severity and age, PTE is associated with worse functional outcomes after severe TBI.

Methods

We performed a retrospective analysis of a prospective database of patients with severe TBI treated from 2002 through 2018 at a single level 1 trauma center. Glasgow Outcome Scale (GOS) was collected at 3, 6, 12, and 24 months postinjury. We used repeated-measures logistic regression predicting GOS, dichotomized as favorable (GOS 4–5) and unfavorable (GOS 1–3), and a separate logistic model predicting mortality at 2 years. We used predictors as defined by the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) base model (i.e., age, pupil reactivity, and GCS motor score), PTE status, and time.

Results

Of 392 patients who survived to discharge, 98 (25%) developed PTE. The proportion of patients with favorable outcomes at 3 months did not differ between those with and without PTE (23% [95% Confidence Interval [CI]: 15%–34%] vs 32% [95% CI: 27%–39%]; $p = 0.11$) but was significantly lower at 6 (33% [95% CI: 23%–44%] vs 46%; [95% CI: 39%–52%] $p = 0.03$), 12 (41% [95% CI: 30%–52%] vs 54% [95% CI: 47%–61%]; $p = 0.03$), and 24 months (40% [95% CI: 47%–61%] vs 55% [95% CI: 47%–63%]; $p = 0.04$). This was driven by higher rates of GOS 2 (vegetative) and 3 (severe disability) outcomes in the PTE group. By 2 years, the incidence of GOS 2 or 3 was double in the PTE group (46% [95% CI: 34%–59%]) compared with that in the non-PTE group (21% [95% CI: 16%–28%]; $p < 0.001$), while mortality was similar (14% [95% CI: 7%–25%] vs 23% [95% CI: 17%–30%]; $p = 0.28$). In multivariate analysis, patients with PTE had lower odds of favorable outcome (odds radio [OR] 0.1; 95% CI: 0.1–0.4; $p < 0.001$), but not mortality (OR 0.9; 95% CI: 0.1–1.9; $p = 0.46$).

Discussion

Posttraumatic epilepsy is associated with impaired recovery from severe TBI and poor functional outcomes. Early screening and treatment of PTE may improve patient outcomes.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CI = confidence interval; **DHC** = decompressive hemicraniectomy; **GCS** = Glasgow Coma Scale; **GOS** = Glasgow Outcome Scale; **IMPACT** = International Mission for Prognosis and Analysis of Clinical Trials in TBI; **OR** = odds radio; **PTE** = posttraumatic epilepsy; **TBI** = traumatic brain injury.

Epilepsy is one of the most common brain conditions affecting nearly 70 million people worldwide.[1] Individuals with epilepsy have diminished quality of life due to the negative cognitive, behavioral, and psychosocial effects of the disease.[2,3] Traumatic brain injury (TBI) is an important risk factor of epilepsy, with posttraumatic epilepsy (PTE) accounting for 20% of symptomatic epilepsy.[3,4] This risk is highest after severe TBI, defined as a postresuscitation Glasgow Coma Scale (GCS) score ≤8, developing in nearly one-third of patients who survive their injury.[5-8]

Although epilepsy significantly contributes to morbidity and mortality in many patient populations,[2,9] the relationship between functional outcomes after TBI and PTE is poorly understood. Patients with TBI demonstrate a remarkable ability for functional recovery, with most patients achieving favorable functional outcomes despite their initial comatose state.[10-12] PTE may impair CNS recovery from TBI, which continues for up to 2 years postinjury.[10]

Previous studies have found an increased risk of mortality[13] and worse functional outcomes[1,14] in PTE. These studies, however, were limited by potential confounding variables,[1,13] limited follow-up periods,[14] small sample sizes,[1,14] and only evaluating patients admitted to rehabilitation hospitals.[1,13,14] To better inform the longitudinal relationship between PTE and functional outcomes, we reviewed a large, modern cohort of patients with severe TBI with systematic outpatient follow-up over 2 years. We tested whether, after controlling for injury severity and age, PTE is associated with worse functional outcomes after severe TBI.

Materials and Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study received approval from the University of Pittsburgh Human Research Protection Office (STUDY19030228). Consent was obtained from subjects' legal representatives. Research procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

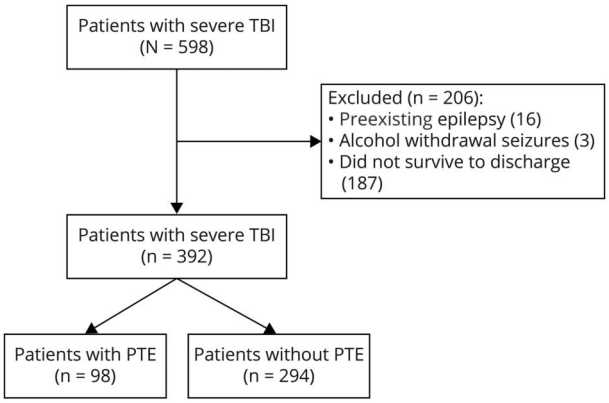
Study Cohort

We performed a retrospective analysis of a prospective database[15] including consecutive patients with severe TBI admitted at a single level 1 trauma center from 2002 through 2018. This database is part of a single-center observational study evaluating the CSF and blood biomarkers of TBI that includes regular and systematic follow-up with outcome assessment. We enrolled all patients admitted during the study period, aged 16–80 years, with a postresuscitation GCS of ≤8, whose legal representative signed consent. Patients were excluded for imminent brain death (GCS 3 with fixed and dilated pupils on presenting examination), pregnancy, and/or penetrating TBI. After enrollment in our database, research personnel prospectively recorded patient characteristics including age, pupil reactivity, GCS score, and neurosurgical procedures. A trained neuropsychologist assessed outcomes at in-person, outpatient follow-up visits at 3, 6, 12, and 24 months posttrauma through a structured interview using the Glasgow Outcome Scale (GOS): 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = low disability.

A board-eligible neurosurgeon (M.P.) accessed the database, maintained by research personnel, and extracted age, pupil reactivity, GCS scale, GOS, and whether the patient underwent a decompressive hemicraniectomy (DHC). M.P. retrospectively reviewed all patient charts to confirm proper inclusion criteria were met; retrospectively collected any missing data; and retrospectively recorded Marshall CT scores, which were not prospectively collected. For the PTE analysis used in this study, we further excluded patients with a medical history of seizures, regardless of etiology, and those who died during index hospitalization.

We retrospectively identified the occurrence and timing of the first late (>7 days) posttraumatic seizure and seizure recurrence (i.e., the second seizure) through evaluating the electronic medical record of our hospital system and nearby systems.[5] We defined a seizure as any clinical event deemed to be a seizure by the treating healthcare team or an electrographic seizure recorded on electroencephalography. Our approach for a retrospective chart review to ascertain seizure timing and occurrence has previously been used in other studies of epilepsy.[6,16] A board-certified epileptologist interpreted all EEGs. Patients typically received a prophylactic 7-day course of phenytoin.[17] The International League Against Epilepsy defines epilepsy as a single seizure with a risk of seizure recurrence of >60% over 10 years. Recognizing the high risk of seizure recurrence after severe TBI, we considered any patient with a single late posttraumatic seizure to have PTE.[5,18,19] In cases where a patient had both an early (≤7 days) and late posttraumatic seizure, the early seizure was considered the first time of seizure occurrence.

Figure 1 Consort Diagram



Statistical Analysis

We summarized baseline clinical characteristics and outcomes using descriptive statistics. We used 2-sided Student *t* test for normally distributed variables and the χ^2 or Fisher exact test for categorical variables.

To predict functional outcomes, our a priori plan was to use ordinal regression to identify associations between PTE and GOS.[20,21] This model violated the proportional odds assumption. Instead, for our primary analysis, we performed a repeated-measures mixed-effects logistic regression with favorable outcomes (GOS 4–5) as the dependent variable. We selected our cutoff point (GOS 1–3 vs 4–5) to be consistent with previous TBI clinical trials and major prognostic studies.[20,22,23]

Before analyzing our data, we decided to control for patient characteristics associated with outcomes by using the same covariates as the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) base model, which includes age, GCS motor score, and pupil reactivity.[23] We considered temporal effects in 2 ways in our models. First, we included time and time squared as candidate predictors, allowing us to account for nonlinear development of PTE. Second, we developed 2 separate model versions, first with PTE as constant, meaning a patient was counted as having PTE regardless of the timing of PTE onset, and second, as time variant, where only patients who already experienced a seizure had PTE. The random effect in our models was the intercept for each patient. Thus, the final mixed-effects models included the following predictors: PTE, age, GCS motor score, pupil reactivity, time, time squared, and a random effect for each patient.

We developed a separate repeated-measures logistic model predicting mortality over the same time frame as our previous models, which did not converge. Instead, we used logistic regression to predict mortality at 2 years. This model included PTE and the IMPACT base model (age, pupil reactivity, and GCS motor score) as predictors.

We performed 2 secondary analyses. First, we evaluated whether changing the cutoff points for favorable outcomes from GOS 4–5 to GOS 5 changed our results. Second, noting that DHC is strongly associated with PTE and a known risk factor of PTE, we developed the same models listed earlier but with DHC as an additional covariate.

In keeping with best practices for outcome studies in TBI, we used multiple imputation to handle missing outcomes data.[24,25] Because we had a nearly complete dataset for predictor variables (see Results section), we used multiple imputation with chained equations to create 20 complete datasets for missing GOS outcomes.[25] For simplicity of reporting results, we reported the raw models without imputation because the average values of our imputed datasets did not meaningfully change our findings. For full transparency, we reported the average of the imputed datasets in eTable 1 (links.lww.com/WNL/C699).

Table 1 Timing of First and Repeat Seizures

		Time to second seizure				
Time to first seizure	**Number of patients**	**0–3 months**	**3–6 months**	**6–12 months**	**12–24 months**	**>24 months**
0–3 months	43	12	4	7	2	5
3–6 months	15	—	4	7	2	1
6–12 months	13	—	—	5	4	0
12–24 months	6	—	—	—	2	2
>24 months	21	—	—	—	—	15

Abbreviations: PTE = posttraumatic epilepsy.
This table displays the timing of the first seizure and seizure recurrence (i.e., second seizure), over the 2-year period in our study. The "number of patients" column displays how many patients had a seizure for each period. For example, 15 patients had a seizure between 3 and 6 months posttrauma. The "time to second seizure" columns display the period for seizure recurrence. For example, of the 15 patients who had their first seizure between 3 and 6 month, 7 patients had seizure recurrence between 6 and 12 months posttrauma. Overall, 77/98 (79%) of patients with PTE in this study developed PTE within 2 years of their index trauma. Of those 77 patients, 50 (65%) had seizure recurrence within 2 years posttrauma.

Table 2 Patient Characteristics

Cohort		Alive at discharge (n = 392)		
Characteristic		**No PTE**	**PTE**	***p* Value**
Number of Patients		294	98	
Age		38 (36–39)	31 (29–34)	**<0.001**
Pupil	Both reactive	76% (222/294%; 70%–80%)	58% (57/98%; 48%–68%)	**<0.01**
	One reactive	9% (28/294%; 6%–13%)	12% (12/98%; 6%–20%)	
	Unreactive	15% (44/294%; 11%–20%)	30% (29/98%; 20%–40%)	
GCS motor	1	22% (64/294%; 17%–27%)	13% (13/98%; 7%–22%)	0.25
	2	6% (19/294%; 4%–10%)	7% (7/98%; 3%–14%)	
	3	11% (31/294%; 7%–15%)	6% (6/98%; 2%–13%)	
	4	18% (53/294%; 14%–23%)	24% (23/98%; 16%–33%)	
	5	40% (118/294%; 34%–46%)	45% (44/98%; 35%–55%)	
	6	3% (9/294%; 1%–6%)	5% (5/98%; 2%–12%)	
DHC		21% (62/294%; 17%–26%)	56% (55/98%; 46%–66%)	**<0.001**
Marshall CT score	1	7% (19/285; 4–10)	1% (1/93%; 0%–6%)	**<0.001**
	2	65% (186/285%; 59%–70%)	48% (45/93%; 38%–59%)	
	3	6% (18/285%; 4%–10%)	11% (10/93%; 5%–19%)	
	4	5% (14/285%; 3%–8%)	9% (8/93%; 4%–16%)	
	5	15% (44/285%; 11%–20%)	31% (29/93%; 22%–42%)	
	6	2% (4/285%; 0%–4%)	0% (0/93%; 0%–4%)	

Abbreviations: DHC = decompressive hemicraniectomy; GCS = Glasgow Coma Scale; PTE = posttraumatic epilepsy.
This chart displays unadjusted characteristics for patients with and without PTE. PTE includes all patients regardless of the timing of their first late seizure. Age is listed as the mean followed by 95% CI in parentheses. All remaining numbers are listed as the percent of total followed by the raw total numbers and 95% CI of the percent total in parentheses.

We tested repeated-measures model assumptions using the Levene test for homogeneity of variance and visual inspection of residuals. We further explored for collinearity between variables, the linearity assumption for continuous variables (age), and outliers.

For all analysis, we used R (Vienna, Austria). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[26]

Data Availability

Deidentified patient data and statistical analyses are available on request of qualified researchers, without time limits, for both new studies and verifying our results. Please email the corresponding author for data sharing requests.

Results

Of the 598 patients with severe TBI in our cohort, 187, 16, and 3 patients were excluded for mortality during index hospitalization, history of seizures, and alcohol withdrawal seizures, respectively (Figure 1). Among the remaining 392 patients, 98 (25%) developed PTE, with 77 (79%) patients having their first seizure within 2 years of trauma. Table 1 summarizes the timing of seizure recurrence (i.e., a second seizure). Seizure recurrence was common with 72/98 (73%) patients having seizure recurrence and 50/77 (65%) patients who had seizures within 2 years also experiencing seizure recurrence within 2 years of trauma (our study period). Because most seizures occurred months to years later in an outpatient setting, most were clinical (92/98; 94%); either purely clinical (84/98; 86%) or electroclinical (8/98; 8%). Only a minority were solely electrographic (6/98; 6%). By 2 years, 48 (12%) patients died.

Table 2 summarizes clinical characteristics and unadjusted associations with PTE. We have a nearly complete dataset with no missing predictor data including age, pupil reactivity, GCS motor score, or DHC. Patients with PTE were younger, had higher rates of unreactive pupils, DHCs, and higher Marshall CT scores ($p < 0.01$).

Our database has robust clinical follow-up, with a median follow-up period of 3.5 years (interquartile range 0.8–8.1 years). Patients had a median of 11 follow-up encounters

Table 3 Outcomes After Posttraumatic Epilepsy

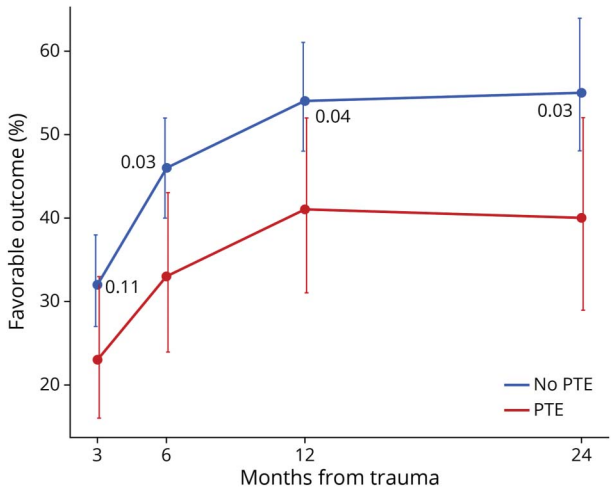
Cohort		Alive at discharge (n = 392)					
		3 months			6 months		
Date		No PTE	PTE	*p* Value	No PTE	PTE	*p* Value
Outcome data available		250	86		242	91	
Missing outcome data		44	12		52	7	
GOS	1	11% (27%; 7%–15%)	0% (0%; 0%–4%)	**<0.001**	14% (35%; 10%–20%)	0% (0%; 0%–4%)	**<0.001**
	2	6% (14%; 3%–9%)	16% (14%; 9%–26%)		1% (2%; 0%–3%)	9% (8%; 4%–17%)	
	3	51% (128%; 45%–58%)	61% (52; 61%)		39% (94%; 33%–45%)	58% (53%; 47%–69%)	
	4	26% (65%; 21%–32%)	19% (16%; 11%–28%)		26% (64%; 21%–32%)	22% (20%; 14%–32%)	
	5	6% (16%; 4%–10%)	4% (4%; 1%–11%)		20% (47%; 15%–25%)	11% (10%; 5%–19%%)	
% Fav.		32% (81%; 27%–39%)	23% (20%; 15%–34%)	0.11	46% (111%; 39%–52%)	33% (30%; 23%–44%)	**0.03**
GOS 2/3		57% (142%; 50%–63%)	76% (66%; 66%–85%)	**<0.01**	40% (96%; 33%–46%)	67% (61%; 56%–77%)	**<0.001**
Mortality		11% (27%; 7%–15%)	0% (0%; 0%–4%)	**<0.001**	14% (35%; 10%–20%)	0% (0%; 0%–4%)	**<0.001**
		12 months			24 months		
Date		No PTE	PTE	*p* Value	No PTE	PTE	*p* Value
Outcome data available		219	83		168	65	
Missing outcome data		75	15		126	33	
GOS	1	16% (36%; 12%–22%)	6% (5%; 2%–14%)	**<0.001**	23% (39%; 17%–30%)	14% (9%; 7%–25%)	**<0.01**
	2	1% (3%; 0%–4%)	6% (5%; 2%–14%)		0% (0%; 0%–2%)	3% (2%; 0%–11%)	
	3	28% (61%; 22%–34%)	47% (39%; 36%–58%)		21% (36%; 15%–28%)	43% (28%; 31%–56%)	
	4	28% (60%; 22%–34%)	24% (20%; 15%–35%)		29% (48%; 22%–36%)	20% (13%; 11%–32%)	
	5	27% (59%; 21%–33%)	17% (14%; 10%–27%)		27% (45%; 20%–34%)	20% (13%; 11%–32%)	
% Fav.		54% (119%; 47%–61%)	41% (34%; 30%–52%)	**0.04**	55% (93%; 48%–63%)	40% (26%; 28%–53%)	**0.04**
GOS 2/3		29% (64%; 23%–36%)	53% (44%; 42%–64%)	**<0.001**	21% (36%; 15%–28%)	46% (30%; 34%–59%)	**<0.001**
Mortality		16% (36%; 12%–22%)	6% (5%; 2%–14%)	**0.02**	23% (39%; 17%–30%)	14% (9%; 7%–25%)	0.28

Abbreviations: GOS = Glasgow Outcome Scale; PTE = posttraumatic epilepsy.
This table summarizes the GOS recorded at 3, 6, 12, and 24 months posttrauma by a trained neuropsychologist stratified by PTE. Patients were classified as having PTE regardless of the onset timing of their late posttraumatic seizures (i.e., a patient who had their first seizure at 1 year is included in the PTE cohort at 3 and 6 months). The effect of PTE timing and GOS is explored in eTable 3 (links.lww.com/WNL/C701), which shows similar effects. Overall, 392 patients are included at each time point. We report the number of patients with outcome data present and missing for each time point when stratified by PTE (98 patients in total) and no PTE (294 patients). Results are displayed as a percentage of total with the total number and 95% confidence interval of percentages in parentheses.

(interquartile range 4–23), excluding the initial inpatient rehabilitation stay.[5] Follow-up rates for recording GOS outcomes were consistent with historical norms from other clinical trials despite excluding patients who died during index hospitalization: 91% at 3 months, 90% at 6 months, 84% at 12 months, and 71% at 24 months.[25]

Table 3 summarizes GOS stratified by PTE at various outpatient follow-up periods. The distribution of GOS was significantly different across PTE groups at all time points ($p < 0.01$). In our cohort, the association of PTE with mortality and favorable outcomes were opposite. Patients with PTE had similar rates of favorable outcomes at 3 months compared with those without PTE (23% [95% CI: 15%–34%] vs 32% [95% CI: 27%–39%]; $p = 0.11$), but lower rates of favorable outcomes at 6 (33% [95% CI: 23%–44%] vs 46% [95% CI: 39%–52%]; $p = 0.03$), 12 (41% [95% CI: 30%–52%] vs 54% ([95% CI: 47%–61%]); $p = 0.02$), and 24 months (40% [95% CI: 47%–61%] vs 55% [95% CI: 47%–63%]; $p = 0.04$) posttrauma. This difference was larger over time (Figure 2). By contrast, patients with PTE had reduced mortality at 3, 6, and 12 months ($p \leq 0.02$), with similar rates of mortality at 24 months (14% [95% CI: 7%–25%] vs 23% [95% CI: 17%–30%]; $p = 0.28$). In eTable 2 (links.lww.com/WNL/C700), we explored whether this effect was confounded by PTE timing and found similar results.

Figure 2 Rates of Favorable Outcomes Over Time



This graph demonstrates the different recovery trajectories of patients with and without posttraumatic epilepsy. The rates of favorable outcomes are similar at 3 months posttrauma ($p = 0.11$) but significantly differ at 6, 12, and 24 months. This difference increases over time as more patients develop seizures.

In a similar vein, patients with PTE had higher rates of persistent vegetative (GOS 2) and severe disability (GOS 3) compared with those without PTE ($p < 0.01$; Figure 3). The differences in rates of GOS 2/3 stratified by PTE status increased over time. By 24 months, the proportion of patients with PTE who had GOS 2–3 was more than double that of patients without PTE (46% [95% CI: 34%–59%] vs 21% [95% CI: 16%–28%]; $p < 0.001$).

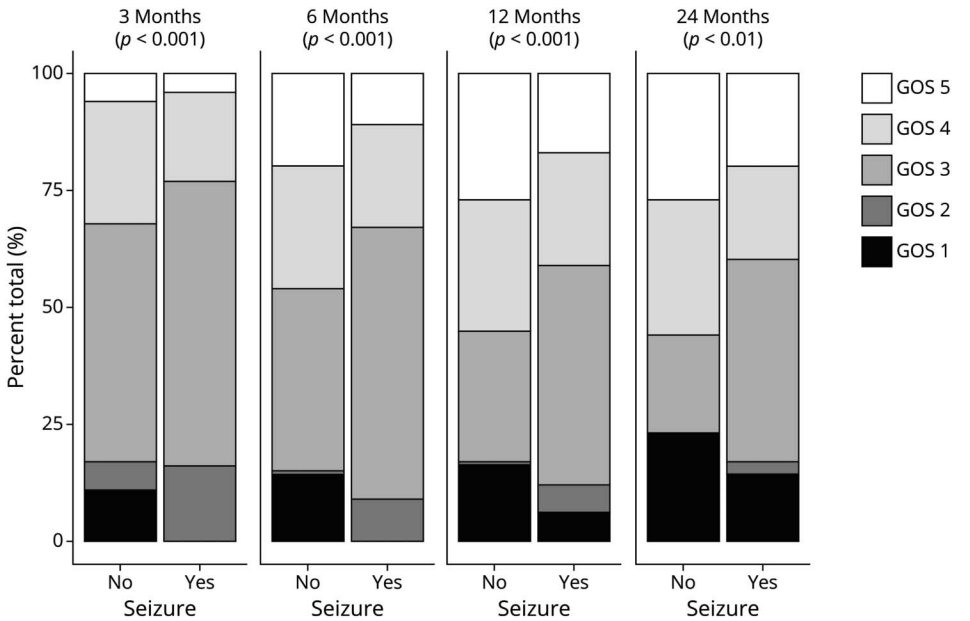
These associations were stable in multivariate modeling (Table 4). After controlling for age, pupil reactivity, and GCS motor score, PTE significantly decreases the rates of favorable outcomes (odds ratio [OR]: 0.1; 95% confidence interval [CI]: 0.1–0.4; $p < 0.001$). By contrast, PTE was not associated with mortality at 2 years (OR: 0.9; 95% CI: 0.1–1.7; $p = 0.46$).

Our secondary analyses did not meaningfully change our results. When exploring alternative cutoff points, PTE (OR 0.4; 95% CI 0.2–0.9; $p = 0.02$) was associated with worse outcomes for GOS 5 vs GOS 1–4, similar to our cutoff of GOS 1–3 vs 4–5. Full details and the model building approach are summarized in eTable 3 (links.lww.com/WNL/C701). Likewise, adding DHC to our models did not change that PTE (OR 0.2; 95% CI 0.1–0.8; $p = 0.03$) reduces rates of favorable outcomes, but does not change mortality (Table 4). By contrast, DHC is associated with both worse functional outcomes and mortality. Imputed datasets and time-varying models that include DHC are summarized in eTable 1 (links.lww.com/WNL/C699).

Discussion

Building on our previous research, we show that, not only is PTE highly prevalent[5] but also highly detrimental to neurologic recovery in modern severe TBI cohorts. After controlling for confounding variables, PTE led to a reduction in favorable outcomes (GOS 4–5) despite similar rates of mortality at 2 years. This difference was largely driven by relatively higher rates of GOS 2–3 over time among patients with PTE compared with those without. That is, patients with PTE are at an increased risk to remain alive in an unfavorable state with impoverished recovery.

Figure 3 Glasgow Outcomes Scale Stratified by Time



For this figure, all patients who developed PTE, regardless of timing, are included in the PTE category. Among patients with PTE, there is a similar rate of favorable outcomes at 3 months ($p = 0.11$). Patients with PTE have significantly lower rates of favorable outcomes at 6, 12, and 24 months posttrauma ($p < 0.05$). Noting that patients with PTE have lower rates of mortality at 3, 6, and 12 months, this effect is driven by higher rates of vegetative (GOS 2) and severe disability (GOS 3) states in patients with PTE compared with patients without PTE ($p < 0.01$). By 24 months, the rate of GOS 2–3 in patients with PTE (46% [95% CI: 34%–59%]) is more than double the rate in patients without PTE (21% [95% CI: 16%–28%]; $p < 0.001$) despite similar mortality rates ($p = 0.11$). GOS = Glasgow Outcome Scale; PTE = posttraumatic epilepsy.

Table 4 Models

Model	Outcome	PTE time varying	Odds ratio (95% confidence interval)								
			Age	*p* Value	GCS motor	*p* Value	Pupil	*p* Value	PTE	*p* Value	DHC	*p* Value
1	Favorable	No	0.3 (0.2–0.5)	**<0.001**	1.9 (1.3–2.7)	**<0.001**	0.3 (0.1–0.6)	**<0.01**	0.1 (0.1–0.4)	**<0.001**	-	-
2	Favorable	Yes	0.4 (0.2–0.5)	**<0.001**	1.9 (1.2–2.6)	**<0.001**	0.3 (0.1–0.5)	**<0.001**	0.1 (0.1–0.3)	**<0.001**	-	-
3	Favorable	No	0.4 (0.2–0.6)	**<0.001**	1.8 (1.3–2.6)	**<0.001**	0.3 (0.1–0.6)	**<0.01**	0.2 (0.1–0.8)	**0.03**	0.1 (0.1–0.4)	**<0.001**
4	Mortality	No	2.0 (1.5–2.5)	**<0.001**	0.7 (0.6–0.9)	**<0.01**	1.3 (0.8–1.9)	0.15	0.9 (0.1–1.7)	0.46	—	—
5	Mortality	Yes	2.0 (1.5–2.5)	**<0.001**	0.7 (0.6–0.9)	**<0.01**	1.3 (0.8–1.9)	0.19	0.9 (0.1–1.7)	0.53	—	—
6	Mortality	No	2.0 (1.5–2.5)	**<0.001**	0.8 (0.6–1.0)	**0.02**	1.3 (0.9–2.0)	0.20	1.0 (0.4–2.8)	0.99	3.1 (1.4–6.8)	**<0.01**

Abbreviations: DHC = decompressive hemicraniectomy; GCS = Glasgow Coma Scale; PTE = posttraumatic epilepsy.
We developed 6 models exploring the relationship between PTE and GOS recorded at 3, 6, 12, and 24 months posttrauma. A repeated-measures ordinal regression model violated the proportional assumption, and thus, we used logistic regression to predict favorable (GOS 4–5) outcomes and mortality. For models 1 and 2, we used a mixed-effects logistic regression with repeated measures. We included time and nonlinear time effects, which were significant in both models. PTE is treated as constant in Model 1, regardless of when the patient developed PTE, while Model 2 treats PTE as time varying. Because our mixed-effects model failed to converge for mortality, we used a generalized linear model (GLM) for Models 4 and 5 predicting mortality within the first 2 years. Model 3 treats PTE as constant, regardless of when a patient developed PTE, whereas Model 4 evaluates only patients who developed PTE within the first 2 years. As a secondary analysis, we controlled for DHC in addition to the IMPACT covariates for favorable outcomes (GOS 4–5; model 3) and mortality (model 6).

The diverging rates of recovery between patients with PTE and those without is best demonstrated in Figure 2. While these results do not prove causality, the effect is biologically plausible. As is the case with many epilepsies, epileptogenic pathways in TBI not only cause spontaneous seizures but also may induce CNS inflammation,[27] neurodegeneration,[28] and, most importantly, beget further seizures.[27,29,30] This self-propagating cycle may underlie the time-dependent divergence of neurologic recovery observed in our study. Early PTE screening and timely treatment may interrupt epileptogenesis and provide an avenue for improving functional outcomes after severe TBI.

Our results suggest that PTE depresses rates of favorable outcomes and is not an epiphenomenon of greater injury severity. While PTE is associated with markers of injury severity including DHC,[5] PTE leads to worse functional outcomes but not mortality. By contrast, DHC, which is a marker of injury severity,[20,21] leads to worse functional outcomes and increased mortality among TBI survivors (Table 4). Of more importance, the rates of favorable outcomes for patients with and without PTE diverge over time, as evidenced in our unadjusted data and models accounting for recovery over time, suggesting that PTE impairs functional recovery. Although our results do not provide causal evidence of depressed recovery in patients with PTE, we provide the most convincing evidence of the deleterious nature of PTE for TBI recovery to date.

Our analysis enhances the prior literature on the relationship between PTE and long-term outcomes. Similar to our results, 2 previous research groups reported worse outcomes among patients with PTE, albeit in smaller cohorts[8,14] with shorter follow-up data.[14] Of importance, our results further add to the current literature by demonstrating that outcomes diverge over time with our repeated-measures study design. Our results do contradict a previous report that found higher rates of mortality among patients with PTE.[13] We believe this difference may be attributable to a lack of control for injury severity in the aforementioned study, which is known to contribute to both PTE and mortality.[3,18,31]

While our study improves the understanding of the relationship between PTE and functional outcomes after TBI, our analysis has several weaknesses. First, we retrospectively collected seizure occurrence, potentially missing several patients with PTE who were lost to follow-up. While our method for retrospectively assessing seizure incidence through chart review has not been prospectively validated, this is a commonly accepted method for studies of both PTE[5,6] and epilepsy in general.[16] Second, despite our efforts to control for confounders, age, pupil reactivity, and GCS motor score account only for approximately one-third of the variance in mortality.[23] While more advance techniques may allow for better accounting for confounding, we are currently limited by the available prognostic models in use today.[23,32] Last, we do not provide insight into the exact cause for depressed recovery after TBI for patients with PTE. Alternate mechanisms, including the negative relationship between outcomes and antiseizure medicines, could explain our effects.[14]

In conclusion, patients with severe TBI with PTE have impaired recovery from their injury with lower rates of favorable outcomes and similar rates of mortality at 2 years. Future studies should prospectively evaluate whether early screening and treatment of PTE leads to improved outcomes after severe TBI.

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Lori Shutter, MD	Departments of Neurology and Critical Care	Drafting/revision of the article for content, including medical writing for content; study concept or design
Niravkumar Barot, MD	Department of Neurology, University of Pittsburgh Medical Center, PA	Drafting/revision of the article for content, including medical writing for content; study concept or design
Jorge Gonzalez-Martinez, MD, PhD	University of Pittsburgh Medical Center, Department of Neurosurgery	Drafting/revision of the article for content, including medical writing for content; study concept or design
James F. Castellano, MD, PhD	University of Pittsburgh Medical Center, Department of Neurology	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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