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Risk Factors and Incidence of Epilepsy after Severe Traumatic Brain Injury

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Abstract

We determined incidence of post-traumatic epilepsy (PTE) after severe traumatic brain injury (TBI). Of 392 patients surviving to discharge, cumulative incidence of PTE was 25% at five years and 32% at fifteen years, an increase compared to historical reports. Among patients with one late seizure (>7 days post-trauma), risk of seizure recurrence was 62% after one year and 82% at ten years. Competing hazards regression identified age, decompressive hemicraniectomy, and intracranial infection as independent predictors of PTE. Patients with severe TBI and a single late post-traumatic seizure will likely require long-term antiseizure medicines.

Keywords

brain trauma; post-traumatic epilepsy; epilepsy; outcome research; seizures

Introduction

Epilepsy affects nearly 70 million people worldwide,¹ and reduces quality of life due to cognitive, behavioral, and psychosocial effects.² In the United States, care for a single patient with epilepsy costs approximately \$50,000 annually.^{3,4}

Traumatic brain injury (TBI) is an important epilepsy risk factor. Post-traumatic epilepsy (PTE) accounts for 5% of all cases of epilepsy and 20% of all symptomatic epilepsy⁴. Risk for PTE is highest after severe TBI, defined as a post-resuscitation Glasgow Coma Scale

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Author Contributions

MWP, EN, JE, DOO, JFC, and JGM contributed to the conception and design of study; MWP, EN, DE, JE, JFC, AP, DOO contributed to the acquisition and analysis of data; MWP, JE, JFC, DOO contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report

(GCS) score of ≤ 8 ,⁴ developing in 10-20% of patients who survive their initial injury.⁵⁻⁷ PTE may develop years after initial injury.⁵

The incidence and risk factors of PTE have not been well characterized in modern cohorts, and definitions have varied.⁸⁻¹¹ According to the International League Against Epilepsy (ILAE), epilepsy is defined as two seizures more than 24 hours apart or one seizure with a risk of seizure recurrence of $>60\%$ after 10 years.¹² Under this operational definition, a single non-acute (i.e., >7 d from initial injury) post-traumatic seizure (PTS) after severe TBI would qualify as epilepsy.¹³ We reviewed a large modern cohort of severe TBI patients with extended outpatient follow-up to determine incidence and risk factors of PTE.

Subjects/Materials and Methods

Study Cohort

The University of Pittsburgh Human Research Protection Office approved this study.

We performed a retrospective analysis of a prospective database including consecutive patients with severe TBI treated at a single Level 1 trauma center from 2002 through 2018.¹⁴ We excluded patients who died during their index hospitalization and those with a past medical history of seizures, regardless of the etiology. Patients were followed at outpatient clinic appointments at 3-, 6-, 12-, and 24-months post-injury and those with persistent neurological problems had continued follow up. We extracted demographic, clinical, and imaging variables from the database.

We retrospectively identified occurrence and timing of first and second PTS. Table 1.A lists operational definitions for early and late PTS, and PTS recurrence. Since many PTS are expected to occur after the index hospitalization, we anticipated most diagnoses to be made clinically rather than electrographically.

Patients typically received 7 days of a prophylactic antiseizure medicines (ASM), usually phenytoin. Continuous video-EEG (cEEG) monitoring was utilized for 3-5 days post-injury and extended at discretion of the treating clinician. A board-certified epileptologist interpreted all cEEG and recorded dates and times of PTS in the electronic health record (EHR). In cases where a seizure was reported in the distant past, we estimated the date of seizure as an average of the period in question (i.e., a seizure occurred “2-3 years ago” would be 2.5 years prior to date of evaluation). After the first late PTS, we recorded new ASM prescriptions and duration of use, excluding subtherapeutic epilepsy dosages for other indications.

To determine last date of follow up and date of death, we searched the EHR of our system and health systems of nearby states. The date of last follow up was the last visit to a healthcare provider, regardless of specialty, that included a medication list. We determined date of death from the EHR. If a patient had ASMs listed in the EHR but no seizure reported, we contacted the patient to clarify medication and seizure history.

Statistical Analysis

We summarized baseline clinical characteristics using descriptive statistics. We reported the number of patients with early and late PTS. To identify characteristics associated with late PTS, we used 2-sided t-tests for normally distributed continuous variables and a chi-squared or Fisher's exact test for categorical variables. We described the cumulative incidence of late PTS and recurrent PTS. We compared cumulative incidence of late PTS between patients with and without early PTS.¹⁵ We then used adjusted Cox regression to identify risk factors for the first late PTS using backwards selection. As a sensitivity analysis, we developed a competing risks regression (CRR) model with the same model inputs using the competing hazard of death. To identify risk factors for recurrent PTS, we used a multivariable Cox regression model, treating the first seizure as a time-varying covariate. We did not use CRR because estimates of subdistribution hazards from time-varying covariates are unreliable.¹⁶ We tested our model assumptions inspecting Schoenfeld and Martingale residuals and the proportional hazards assumption. For all analysis, we used R (Vienna, Austria) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.¹⁷

Results

Overall, 598 patients presented with severe TBI, of whom 192 died before discharge, 12 had pre-existing epilepsy, and 2 had a history of alcohol withdrawal seizures (Figure 1). Among 392 included patients, 18 had early PTS; 98 had late PTS (72/98 had recurrent PTS, 26/98 had a single late PTS); and 55 died during the study period. Overall, median follow up was 3.5 years (interquartile range [IQR]: 0.8 – 8.1 years), during which patients had a median of 11 follow-up encounters (IQR: 4 – 23), excluding the initial inpatient rehabilitation stay.

The rate of early PTS was 5% (n=18). Cumulative incidence amongst TBI survivors for late PTS was 25% (95% Confidence Interval [CI]: 22–27%) at five years and 32% (95% CI: 29–35%) at fifteen years (Figure 2). Risk of seizure recurrence was 61% (95% CI: 57–66%) at two years and 82% (95% CI: 77–87) at ten years. Among patients with early PTS, the risk of a late PTS was 44% (95% CI: 32–57%) at 2 years, which was higher than the rate among patients without early PTS (p=0.01).

All but seven patients were started on ASMs after their first late PTS. These seven patients, all of whom had PTS recurrence, were not started on an ASMs because they did not seek medical attention until after repeat PTS (4); had seizures in the setting of cocaine use (1) or shunt malfunction (1); and one had a questionable PTS and was started on ASMs after a repeat PTS. Nine patients were started on multiple ASMs due to pharmacoresistance. Of patients with recurrent seizures, 25 were off ASMs of the time of PTS recurrence. These patients were not on ASMs because they were never started (7), ran out of ASMs or self-discontinued (6), or were weaned by their healthcare provider (12). Overall, 23/98 patients with PTS were on multiple ASMs at the time of last follow up.

Table 1.B and 1.C summarize clinical characteristics and unadjusted associations with the first late PTS and PTS recurrence, respectively. Our multivariate models found age, DHC,

and CNS infection to increase the risk for PTS (Table 1.D). Shunt dependency and female gender decreased the risk for PTS recurrence.

Discussion

In a modern cohort of severe TBI patients, we identified a cumulative incidence of PTS of 25% at five years and 32% at fifteen years. Including patients from the 1930s to 1980s, Annegers et al. first described the rates of PTS after severe TBI at approximately 10% at five years and increasing to 17% at twenty years.⁵ Subsequent groups have described higher rates of PTS of 14-17% from 2-3 years post-injury^{6,8} and 21% at five years.⁹ Previous evaluations have had several drawbacks: (1) cohorts from prior decades with presumably worse survival and more limited means of monitoring for seizures;^{6,8,9} (2) short-term follow up;^{6,8,10,18} (3) non-standardized definitions of severe TBI, PTS and PTE;^{8,11} and (4) small sample sizes.¹⁸ Our reported rates of PTS (25% at five years and 32% at fifteen years) are substantially higher than previous reports.

Additionally, we identified several risk factors including DHC, age, and CNS infection for the first late PTS and male gender and shunt independence for PTS recurrence. Previous reports found penetrating injury, depressed skull fractures, and cerebral contusions to be associated with PTE.^{1,2} These are markers of injury severity, similar to our findings. The increased incidence of PTE, coupled with reliable risk factors, encourages the utilization of severe TBI as not only a model of epileptogenesis but also as a screen for anti-epileptogenic therapeutics.

We identified a long-term, high risk (82% at 10 years) of seizure recurrence, with a majority (62%) of patients having seizure recurrence within one year. Within the context of current ILAE definitions,¹⁹ this validates our proposed definition of post-traumatic epilepsy as a single late seizure after severe TBI. Similarly, patients with an early PTS were at increased risk of late PTE (44% by two years). This finding contradicts previous reports⁹ stating that only immediate PTS (i.e., within 24 hours of trauma), and not early PTS, predict late PTS. Taken together, patients with any PTS should be carefully monitored for seizure recurrence, especially in the setting of aforementioned risk factors. Patients with a single late PTS should be diagnosed with epilepsy and promptly treated with ASMs.

Our study has several limitations, including retrospective nature and single center. We employed a passive surveillance for seizures, which may under-report the true incidence of PTE.

In conclusion, we demonstrated the incidence of post-traumatic epilepsy may be increasing over time with improvements in acute and post-acute care, as well as overall patient survival. After a single post-traumatic seizure, patients with severe TBI should be referred to an epileptologist for consideration of long-term anti-epileptic therapy and close follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

All data and statistical analyses are available from the authors upon request of qualified researchers.

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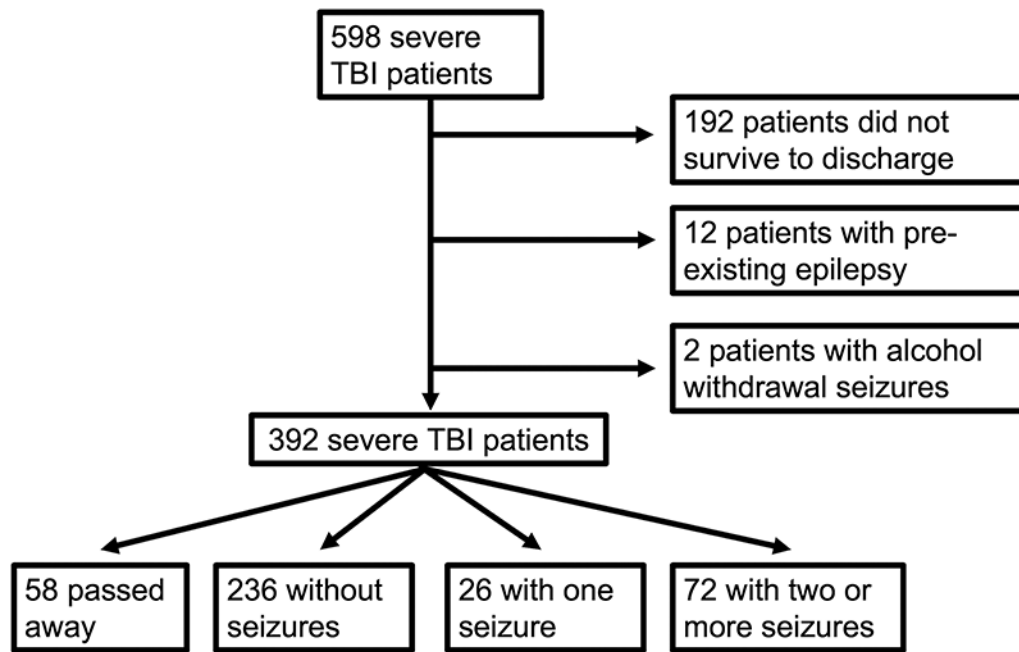
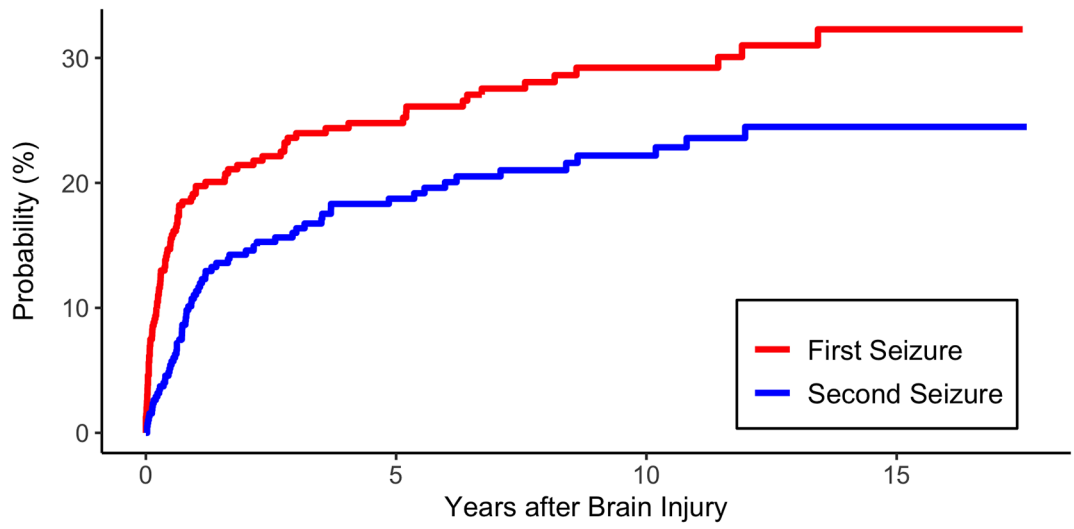


Figure 1. Consort Diagram. Outline of patient accrual and exclusions.



Number at risk

392	146	77	15
392	162	88	20

Figure 2.A.
Cumulative Incidence of the first PTS and second PTS. Time zero is the date of trauma.

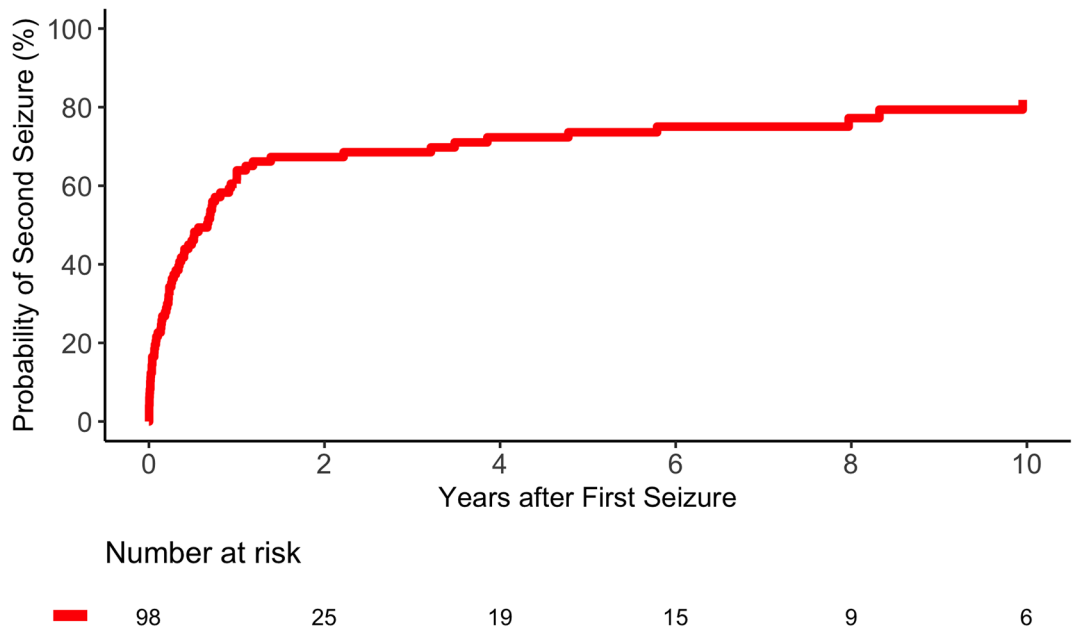


Figure 2.B.

Cumulative Incidence of Seizure Recurrence. Figure 2.B shows the cumulative incidence of PTS recurrence with time zero as the time of first late PTS. The international league against epilepsy (ILAE) defines epilepsy as two seizures more than 24 hours apart or one seizure with a risk of seizure recurrence of >60% after 10 years. With a risk of seizure recurrence of 82% after ten years, a single late PTS meets the ILAE definition of epilepsy.

Table 1.A

Definitions of terms used in the manuscript

Term	Abbreviation	Definition
Post-traumatic seizure	PTS	A clinical event deemed to be a seizure by the treating healthcare team or an electrographic seizure on electroencephalography (EEG)
Early PTS		PTS occurring within 7 days from the date of trauma
Late PTS		Any PTS after 7 days from the date of trauma
Post-traumatic epilepsy	PTE	A single late post-traumatic seizure
PTS recurrence		A second late PTS among patients who have already had a late PTS

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Table 1.B

Predictors of late PTS. This table reflects timing of the first late PTS and not PTS recurrence. Although the likelihood of observing a late PTS is affected by length of follow up, the effect is minimal and explored in Supplementary Table 1. For p-values, we used 2-sided t-tests for normally distributed continuous variables and a chi-squared or Fisher's exact test for categorical variables. CNS infection is any culture positive infection of the CNS that occurred within 3 months of trauma.

Description		No Late PTS (n=294)	Late PTS (n=98)	p-value	
	Age	38 +/- 16	31 +/- 14	<0.001	
Demographic	Race	American Indian	1/294 (0.3%)	1/98 (1%)	0.22
		Asian/Indian	4/294 (1.4%)	0/98 (0%)	
		Black	24/294 (8%)	3/98 (3%)	
		White	264/294 (90%)	94/98 (96%)	
		Other	1/294 (0.3%)	0/98 (0%)	
Clinical	GCS	3	37/292 (13%)	13/98 (13%)	0.29
		4	22/292 (7%)	7/98 (7%)	
		5	33/292 (11%)	6/98 (6%)	
		6	49/292 (17%)	23/98 (24%)	
		7	121/292 (41%)	44/98 (45%)	
		8	30/292 (11%)	5/98 (5%)	
		Hypoxia	37/284 (13%)	12/92 (13%)	0.99
		Hypotension	68/282 (24%)	17/93 (18%)	0.24
		Major extracranial injury	45/281 (16%)	9/93 (10%)	0.13
		EVD hemorrhage	33/288 (11%)	11/96 (11%)	0.99
		CNS Infection	23/294 (8%)	19/98 (19%)	0.001
		DHC	62/294 (21%)	55/98 (56%)	<0.001
		Craniotomy	89/294 (30%)	65/98 (66%)	<0.001
		Shunt	35/294 (12%)	30/98 (31%)	<0.001
		Lobectomy	6/294 (2%)	17/98 (17%)	<0.001
	LOS	24 +/- 15	28 +/- 13	0.002	
	ICU LOS	17 +/- 9	21 +/- 10	0.001	
Laboratory	Glucose	156 +/- 61	158 +/- 60	0.79	
	Hemoglobin	13.2 +/- 2.2	13.4 +/- 1.8	0.57	
	INR	1.2 +/- 0.3	1.2 +/- 0.3	0.47	
	Intoxicated	117/245 (48%)	38/76 (50%)	0.78	
Radiographic	SDH	104/290 (36%)	50/96 (52%)	0.005	
	EDH	30/286 (10%)	13/93 (14%)	0.36	
	tSAH	222/286 (78%)	72/93 (77%)	0.97	
	IVH	53/288 (18%)	20/95 (21%)	0.57	
	Contusion	157/288 (55%)	61/96 (64%)	0.12	
	Depressed Skull Fracture	35/288 (12%)	23/96 (24%)	0.005	

Description		No Late PTS (n=294)	Late PTS (n=98)	p-value
Petechial hemorrhage		184/288 (69%)	58/87 (67%)	0.70
Obliteration of the 3 rd ventricle		36/267 (13%)	27/87 (31%)	<0.001
Midline Shift		73/267 (13%)	27/87 (31%)	<0.001
MLS > 5mm		45/290 (16%)	28/96 (29%)	<0.01
Marshall CT score	1	19/285 (7%)	1/93 (1%)	<0.001
	2	186/285 (65%)	45/93 (48%)	
	3	18/285 (6%)	10/93 (11%)	
	4	14/285 (5%)	8/93 (9%)	
	5	44/285 (15%)	29/93 (31%)	
	6	4/285 (2%)	0/93 (0%)	

EVD – External ventricular drain

DHC – Decompressive hemicraniectomy

LOS – Length of Stay

ICU – Intensive Care Unit

INR – International Normalized Ratio

SDH – Subdural hematoma

EDH – Epidural hematoma

tSAH – Traumatic subarachnoid hemorrhage

IVH – Intraventricular hemorrhage

MLS – Midline shift

Table 1.C

Predictors of PTS Recurrence. We report predictors of PTS recurrence (i.e., a second PTS). Although the likelihood of PTS recurrence varies by follow-up time, the effect is minimal and explored in Supplementary Table 2. Time zero is the time of the first late PTS. For p-values, we used 2-sided t-tests for normally distributed continuous variables and a chi-squared or Fisher's exact test for categorical variables.

Description		No PTS Recurrence (n=26)	PTS Recurrence (n=72)	p-value	
	Age	36 +/- 16	30 +/- 12	0.07	
Demographic	Race	American Indian	1/26 (4%)	0/72 (0%)	0.39
		Asian/Indian	0/26 (0%)	0/72 (0%)	
		Black	1/26 (4%)	2/72 (3%)	
		White	24/26 (92%)	70/72 (97%)	
		Other	0/26 (0%)	0/72 (0%)	
	Sex (male)	18/26 (69%)	62/72 (86%)	0.08	
Clinical	GCS	3	5/26 (19%)	8/72 (11%)	0.35
		4	2/26 (8%)	5/72 (7%)	
		5	3/26 (11%)	3/72 (4%)	
		6	7/26 (27%)	16/72 (22%)	
		7	9/26 (35%)	35/72 (49%)	
		8	0/26 (0%)	5/72 (7%)	
		Hypoxia	5/25 (20%)	7/67 (10%)	0.30
		Hypotension	6/26 (23%)	11/67 (16%)	0.55
		Major extracranial injury	3/26 (12%)	6/67 (9%)	0.71
		EVD hemorrhage	3/25 (12%)	8/71 (11%)	0.99
		CNS Infection	5/26 (19%)	14/72 (19%)	0.98
		DHC	11/26 (42%)	44/72 (61%)	0.10
		Craniotomy	15/26 (58%)	50/72 (69%)	0.28
		Shunt	10/26 (38%)	20/72 (28%)	0.31
		Lobectomy	3/26 (12%)	14/72 (19%)	0.55
	LOS	29 +/- 13	27 +/- 13	0.59	
	ICU LOS	23 +/- 9	21 +/- 10	0.33	
Laboratory	Glucose	136 +/- 40	165 +/- 65	0.01	
	Hemoglobin	13.0 +/- 1.8	13.5 +/- 1.8	0.27	
	INR	1.2 +/- 0.3	1.2 +/- 0.2	0.60	
	Intoxicated	13/20 (65%)	25/56 (45%)	0.12	
Radiographic	SDH	14/26 (54%)	36/70 (51%)	0.83	
	EDH	4/25 (16%)	9/68 (13%)	0.74	
	tSAH	19/25 (76%)	53/68 (78%)	0.84	
	IVH	5/25 (20%)	15/70 (21%)	0.88	
	Contusion	16/26 (62%)	45/70 (64%)	0.80	

Description		No PTS Recurrence (n=26)	PTS Recurrence (n=72)	p-value
Depressed Skull Fracture		7/26 (27%)	16/70 (23%)	0.68
Petechial hemorrhage		14/23 (61%)	44/64 (69%)	0.49
Obliteration of the 3 rd ventricle		7/23 (30%)	20/64 (31%)	0.94
Midline Shift		9/26 (35%)	31/70 (44%)	0.45
MLS > 5mm		6/26 (23%)	22/70 (31%)	0.42
Marshall CT score	1	1/25 (4%)	0/68 (0%)	0.36
	2	12/25 (48%)	33/68 (49%)	
	3	1/25 (4%)	9/68 (13%)	
	4	3/25 (12%)	5/68 (7%)	
	5	8/25 (32%)	21/68 (31%)	
	6	0/25 (0%)	0/68 (0%)	

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Table 1.D

Models for risk factors for first late PTS (i.e., PTE) and PTS Recurrence. The first model is a Cox Proportional Hazards (CPH) model predicting the first late PTS (i.e., PTE). As a sensitivity analysis, we developed a competing risks regression using the same inputs as our first model and modeling the competing hazard of death. Both models predict the occurrence of the first late PTS. Our third model predicts PTS recurrence, or the second PTS. In this last model, we include the occurrence of a first late PTS as a time-varying covariate, as the first late PTS occurs during follow up and, by definition, prior to PTS recurrence. *The CRR model reports the subdistribution hazard.

Cumulative Incidence	Model Type	Variable	Hazard Ratio*	95% CI		P-value
First late PTS (PTE)	CPH	DHC	4.1	2.2	6.1	<0.001
		CNS Infection	1.7	1.2	2.3	0.04
		Age (decade)	0.7	0.6	0.9	<0.001
First late PTS (PTE)	CRR	DHC	4.4	3.7	4.9	<0.001
		CNS Infection	1.7	1.2	2.2	0.03
		Age (decade)	0.7	0.6	0.9	<0.001
PTS Recurrence	CPH with time-varying coefficient	Shunt Dependence	0.6	0.3	1.0	0.04
		Sex (male)	2.7	1.4	5.3	<0.01