Prognostic Models for Predicting Post-Traumatic Seizures During Acute Hospitalization, and at 1 and 2 Years Following Traumatic Brain Injury

Anne C Ritter[1, 2], Amy K Wagner[2,3,4,5], Jerzy P Szaflarski[6], Maria M Brooks[1], Ross D Zafonte[7], Mary Jo Pugh[8,9], Anthony Fabio[1], Flora M Hammond[10,11], Laura E Dreer[12], Tamara Bushnik[13], William C Walker[14], Allen W Brown[15], Doug Johnson-Greene[16], Timothy Shea[17], Jason W Krellman[18], Joseph A Rosenthal[19]

[1]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA
[2]Physical Medicine & Rehabilitation, University of Pittsburgh, Pittsburgh, PA
[3]Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA
[4]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA
[5]Center for Neuroscience at University of Pittsburgh, Pittsburgh, PA
[6]University of Alabama at Birmingham Epilepsy Center, Department of Neurology, University of Alabama, Birmingham, AL
[7]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA
[8]South Texas Veterans Health Care System Polytrauma Rehabilitation Center, San Antonio, TX
[9]Department of Epidemiology and Biostatistics, University of TX Health Science Center San Antonio, San Antonio, TX
[10]Carolinas Rehabilitation, Charlotte, NC
[11]Indiana University School of Medicine, Indianapolis, IN
[12]Departments of Physical Medicine and Rehabilitation and Ophthalmology, University of Alabama, Birmingham, AL
[13]Rusk Rehabilitation, New York University School of Medicine, New York, NY
[14]Dept of Physical Medicine & Rehabilitation, Virginia Commonwealth University
[15]Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN
[16]Miller School of Medicine, University of Miami, Miami, FL
[17]Department of Physical Medicine and Rehabilitation, Ohio State University, Columbus, OH
[18]Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY
[19]Department of Physical Medicine and Rehabilitation, Ohio State University, Columbus, OH

Corresponding Author:
Amy K Wagner, MD
3471 Fifth Avenue Suite 202
Dept. Physical Medicine and Rehabilitation
University of Pittsburgh
Pittsburgh PA 15213
412-648-6666
wagnerak@upmc.edu

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Abstract

Objective: Post-traumatic seizures (PTS) are well-recognized acute and chronic complications of traumatic brain injury (TBI). Risk factors have been identified, but considerable variability in who develops PTS remains. Existing PTS prognostic models are not widely adopted for clinical use and do not reflect current trends in injury, diagnosis, or care. We aimed to develop and internally validate preliminary prognostic regression models to predict PTS during acute care hospitalization, and at Year-1 and Year-2 post-injury.

Methods: Prognostic models predicting PTS during acute care hospitalization and Year-1 and Year-2 post-injury were developed using a recent (TBI 2011-2014) cohort from the TBI Model Systems National Database. Potential PTS predictors were selected based on previous literature and biological plausibility. Bivariable logistic regression identified variables with a p-value<0.20 that were used to fit initial prognostic models. Multivariable logistic regression modeling with backward-stepwise elimination was used to determine reduced prognostic models and to internally validate using 1000 bootstrap samples. Fit statistics were calculated, correcting for over-fitting (optimism).

Results: Sex, craniotomy, contusion load, and pre-injury limitation in learning/remembering/concentrating were significant PTS predictors during acute hospitalization. Significant PTS predictors at Year-1 were subdural hematoma (SDH), contusion load, craniotomy, craniectomy, seizure during acute hospitalization, post-traumatic amnesia duration, pre-injury mental health treatment/psychiatric hospitalization, and pre-injury incarceration. Year-2 significant predictors were similar to Year-1: SDH, intraparenchymal fragment, craniotomy, craniectomy, seizure during acute hospitalization, and pre-injury incarceration. Corrected concordance (C) statistics were 0.599, 0.747, and 0.716 for acute hospitalization, Year-1, and Year-2 models, respectively.

Significance: The prognostic model for PTS during acute hospitalization did not discriminate well. Year-1 and Year-2 models showed fair to good predictive validity for PTS. Cranial surgery, while medically necessary, requires ongoing research regarding potential benefits of increased monitoring for signs of epileptogenesis, PTS prophylaxis, and/or rehabilitation/social support. Future studies should externally validate models and determine clinical utility.

Keywords:
Epilepsy, TBI Model System, Prognostic modeling, Risk factors, Craniectomy

Introduction

Traumatic brain injury (TBI) is a well-recognized public health problem. Over 2.5 million TBIs occur annually in the United States[1]; approximately 11% require hospitalization, primarily for moderate/severe injury. TBI is increasingly recognized as a chronic disease, significantly impacting morbidity and mortality[2;3]. As medicine advances, more individuals are expected to survive moderate/severe TBI, increasing the number affected by injury-associated complications.

Post-traumatic seizures (PTS) and epilepsy (PTE) are well-recognized TBI complications. PTS can develop at any point after TBI and is classified by time of first seizure (immediate: <24hrs, early: 24hrs to 7d, and late: >7d post-TBI). Immediate and early PTS are considered provoked: directly related to the primary injury. Late seizures are attributed to secondary injury cascades and persistent epileptogenic mechanisms, and if recurrent and otherwise unprovoked, represent PTE[4;5]. PTS incidence and prevalence vary widely throughout the literature and depend on study design (e.g. length of follow-up), population characteristics (e.g. injury severity), and PTS definition. Previous reports after primarily closed-head injury indicate a broad range of percent affected (early: 1.4-12%; late: 4.4-18.9%)[6-11]. Work using the Traumatic Brain Injury Model System (TBIMS) National Database, including individuals with predominantly closed-head moderate/severe TBI, demonstrated prevalence rates of 8.9% and 1.8% for immediate and early PTS, respectively[12]. By 1yr post-injury, 20.4% of the cohort reported seizures, 12% met criteria for late PTS (i.e. PTE). Late PTS prevalence at 2yrs and 5yrs post-TBI increased to 16.8% and 20.5%[12]. Incident seizure risk after severe TBI, beyond 10yrs post-injury, remains significantly elevated versus the general population[6]. These data suggest epileptogenesis can follow a prolonged course, and TBI related pathology exerts long-term epileptogenic effects.

Prognostic models can estimate an individual's risk for developing an outcome of interest based on specific characteristics[13]. While many studies examined injury characteristics and associations with PTS, few have developed prognostic PTS models. Of these, none have been integrated into routine clinical practice. Such models were developed decades ago, using small samples, and examining probability based on a single risk factor[14;15]. A multivariable mathematical model was developed in the

1970's and validated using datasets from TBI studies available at the time[16]. However, these prognostic models do not reflect current trends in injury severity, TBI detection and treatment, or seizure prophylaxis. Since then, improved neuroimaging allows greater specificity when characterizing intracranial pathology. Neurosurgical procedures, including craniectomy, are now more common for treating intracranial pathology. Therefore, new prognostic models reflecting current injury, diagnosis, and treatment trends are required if models are to be clinically useful. Accurate PTS risk prediction could help define high-risk populations in support of clinical intervention trials. Predictive models could also inform clinical algorithms to identify individuals likely to benefit from tailored seizure prophylaxis or treatment.

The TBIMS National Database (TBIMS-ND) is an ongoing, multi-center, longitudinal observational study. Currently, there are 16 funded centers collecting demographic, premorbid personal and medical history, and injury-specific data upon study enrollment, as well as chronic medical conditions, psychosocial, and rehabilitation outcomes. The TBIMS-ND is an excellent source of data for prognostic model development involving a variety of TBI-related outcomes for individuals surviving acute injury and receiving inpatient rehabilitation. Therefore, the aim of this study was to develop and internally validate prognostic models predicting PTS during acute care hospitalization, at Year-1, and Year-2 post-injury for a recent cohort in the TBIMS-ND.

Methods

Study Design and Population

Data were obtained from the TBIMS-ND. All participating centers have a Level-I or Level-II Trauma Center, acute neurosurgical capabilities, and associated comprehensive inpatient TBI rehabilitation. Individuals with moderate/severe TBI [Post-traumatic Amnesia (PTA)>24hrs, or Loss of consciousness (LOC)>30min, or emergency department Glasgow Coma Scale (GCS) score<13, or positive neuroimaging findings)], admitted to a participating hospital emergency department within 72hrs of injury, age ≥16yrs, receiving acute care and inpatient rehabilitation within a TBIMS designated

hospital system were eligible for study inclusion. Patients participating in TBIMS rehabilitation centers (defined as having brain tissue injury due to an external blow or force to the head) are referred from their affiliated level 1 trauma centers and meet criteria for participation in acute inpatient rehabilitation, which is typically defined by assessing patient ability to benefit from, and participate in, a multidisciplinary therapy program such that progress during acute inpatient rehabilitation would result in a community-based discharge plan. While specific referral patterns may vary somewhat from center to center, referral is made on clinical grounds, and the TBIMS-ND is considered to be largely representative of individuals with TBI admitted to acute rehabilitation facilities nationally[17]. All subjects, or legal proxy, provided written informed consent to participate in each center's Institutional Review Board approved protocol for TBIMS-ND data collection.

Varied definitions for PTS were used at different times within the TBIMS-ND, with the most recent variable change occurring in 2012. For consistency with data definitions, and to ensure analyzed data reflect current population trends and standards of care, current analyses included participants injured between October 1, 2011 and August 31, 2014. Multiple pre-injury predictors of interest were not collected until Year-1 follow-up, particularly pre-index injury (aka premorbid) TBI. Therefore, individuals injured during this time frame, but not yet eligible for Year-1 follow-up, were excluded from analyses

Data Collection

Data were limited to those collected at enrollment, Year-1, or Year-2 post-injury. All data were collected using standardized protocols. Enrollment data, collected though chart review and interview, included demographic, social, and injury characteristics, International Classification of Disease revision 9 (ICD-9) codes, pre-injury personal and medical history, and acute hospitalization outcomes. CT scan data were classified by trained raters based on a composite of the worst findings on CT scan over the first 7 days post-injury. Prospective follow-up data were collected via a semi-structured telephone administered battery. Proxy interviews were completed if an individual with TBI could not provide reliable responses. A comprehensive syllabus containing data collection definitions and protocols is

provided at https://www.tbindsc.org/Syllabus.aspx. All data collectors receive extensive training and undergo periodic quality assessments from the TBIMS National Data Center to ensure high fidelity with data collection protocols and adherence to data collection definitions.

Outcome Variable

PTS status, dichotomized as seizure activity present or absent, was the main outcome, determined during the course of acute hospitalization, at Year-1, and Year-2.

Following discharge from acute hospitalization, TBIMS Center data collectors record up to 20 ICD-9 codes in the participant's medical chart related to their TBI admission. To determine PTS status during acute hospitalization, all recorded acute care ICD-9 codes were reviewed. ICD-9 codes relating to convulsion (780.39), PTS (780.33), and epilepsy (345.0x→345.9x) were included as evidence of seizure following TBI.

PTS status at Year-1 and Year-2 were determined prospectively solely via participant (or proxy) self-report. Study participants were asked "*Have you had a seizure since your TBI?*" at follow-up interviews. If participants answered yes, they were asked, "*Since your discharge from rehabilitation, have you had a seizure?*" at Year-1 and, "*In the past year, have you had a seizure?*" at the Year-2 follow-up interview. If patients answered yes to the second question, they were counted as having PTS at Year-1 and Year-2, respectively. Year-1 and Year-2 PTS status were independent of acute hospitalization PTS status, and recurrent seizures at Year-1 and Year-2 are reported.

Predictors of Interest

Predictors of interest included baseline demographics, personal and medical history information, and injury characteristics. All predictors were selected *a priori* based on biological plausibility and possible risk factors identified in previous literature[6-9;18-20] (**Table 1**). Demographic variables included age, sex, and race. Personal and medical history variables included *pre-injury*: prior TBI, prior TBI with LOC, prior moderate/severe TBI, conditions significantly limiting physical activity, limitation in learning, remembering, or concentrating, mental health (MH) treatment, psychiatric hospitalization, suicide attempt, drug use, alcohol risk, military service, military combat, and incarceration. Alcohol risk was

based on self-report and classified into safe, at risk, or heavy use, adapted from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) definitions. Drug use did not delineate specific substances used.

Injury characteristics included injury severity, duration of post-traumatic amnesia (PTA) in Year-1 and Year-2 models, confirmed pathology on CT scan, intraparenchymal fragment, penetrating TBI (pTBI), craniotomy, craniectomy, and spinal cord injury (**Table 1**). CT findings were included as separate variables for specific pathology type [e.g. subdural hematoma (SDH), epidural hematoma (EDH)], coded as present or absent and were not mutually exclusive. pTBI was computed via a coding algorithm previously validated in a subsample of the TBIMS[21]. Also, a contusion load score was calculated by summing the number of regions with reported contusion (**Table 1**). This score was collapsed into 0, 1, 2, 3, and 4 or more regions. Acute alcohol use was classified based on ICD-9 codes during acute hospitalization (**Table 1**). At Year-1 and Year-2, seizure during acute hospitalization was included as a risk factor. No data were collected on premorbid seizure activity or history of epilepsy.

Prognostic Modeling

Multivariable logistic regression was used to generate prognostic models for PTS during acute hospitalization, Year-1, and Year-2; models were internally validated with resampling. For each time-point (PTS during acute hospitalization, PTS status since discharge from rehabilitation [Year-1], and PTS status in the past year [Year-2]), all potential risk factors described above were first examined using bivariate logistic regression. All variables with p-value<0.20 were retained for inclusion in multivariable model building.

A saturated (multivariable) logistic regression model, including all variables identified in the above step, was fit for each PTS time-point. After fitting a saturated model, variables were preliminarily examined for multicollinearity using Spearman correlation matrices. For each model, retained fragment and pTBI were highly collinear ($r>0.9$); pTBI occurred much less frequently versus retained fragment, and therefore, was not included in further prognostic modeling. Premorbid history of MH disorder and premorbid psychiatric hospitalization were also highly collinear and were combined to form a four-level

categorical variable (no MH disorder or hospitalization; MH disorder no hospitalization; hospitalization without MH disorder; both MH disorder and hospitalization). The saturated model was refit, and variance inflation factors (VIF) and condition indices were calculated. Correlations between age and other predictor variables were explored, however, VIF values did not indicated problematic multicollinearity when age was included in each model.

Next, backward (step-down) variable selection was performed with an exit criterion of alpha=0.05. The reduced model was internally validated via resampling in an automated process using the *rms: Regression Modeling Strategies* package for R[22]. Specifically, 1,000 bootstrap samples were drawn with replacement from the original data such that each bootstrap sample had an equal number of observations as the original dataset. In each bootstrap sample, backward elimination with an exit criterion of alpha=0.05, was used to validate the reduced model. The C-statistic, a measure of concordance equal to the area under the receiver operating characteristic (ROC) curve, was calculated using Somers' D_{xy} for the saturated model[23]. The C-statistic was calculated for the final, reduced model selected from the original data, with and without adjustment for optimism.

All statistical analyses were completed using SAS version 9.4 (SAS Institute, Cary NC) and R version 3.0.3[24].

Results

Population

2,136 participants injured October 1, 2011 through August 21, 2014 had ICD-9 codes from acute hospitalization recorded, which were used to determine PTS during acute hospitalization (**Supplemental Figure 1**). Of these, 2,042 had data available on all predictors identified in simple logistic regression for seizure during acute hospitalization. Some individuals in this study population had not yet reached their Year-1 or Year-2 follow-up time-point at the time of analysis. At Year-1, 2,079 participants had PTS data, and 1,933 participants had data available for all predictors included in the saturated regression model. For Year-2 analyses, 1,364 participants had PTS data, and 1,276 had data for predictors included in the saturated model. At each time point, demographic and clinical variables

were similar to previous TBI studies (**Table 2**). Based on these data, 91% of the population with seizure data during acute hospitalization was used to generate Year-1 prognostic models, and 60% of the population at acute hospitalization was used to generate Year-2 prognostic models. The Year-2 sample size is smaller than acute and Year-1 samples, due to many subjects not yet reaching their Year-2 follow-up time point.

Prognostic Models

Following bivariate examination of predictors, 15 variables met inclusion criteria ($p<0.20$) for the initial, saturated prognostic model of PTS during acute hospitalization (**Supplemental Table 1)**. After backward elimination and bootstrapping, the final model included sex, pre-injury limitation in learning/concentrating/remembering, contusion load, and craniotomy. Craniotomy was among the most statistically significant predictors in the final prognostic model and was selected in 85% of bootstrapped models (**Supplemental Table 1**). After correction for optimism, the C-statistic in the final model was 0.599 (**Table 3**).

The Year-1 saturated prognostic model of PTS included 22 predictor variables (**Table 4**). After validation, the final model included injury severity, SDH, contusion load, craniotomy, craniectomy, seizure during acute hospitalization, pre-injury condition limiting physical activity, pre-injury MH treatment/psychiatric hospitalization, and incarceration. Craniectomy was the most statistically significant predictor and was selected in 100% of bootstrap samples (**Table 4, Figure 1**). After adjustment for optimism, the calculated C-statistic for the Year-1 model was 0.747 (**Table 3**).

The Year-2 saturated model included 21 predictor variables (**Table 5)**. After validation, SDH, intraparenchymal fragment, craniotomy, craniectomy, seizure during acute hospitalization, and pre-injury incarceration were retained. Acute hospitalization seizure and craniectomy were the most statistically significant predictors of PTS at Year-2 and were selected in 99 and 95% of bootstrap samples, retrospectively. After correction for optimism, the C-statistic was 0.716 (**Table 3**).

Discussion

Over time, observational studies have identified relevant clinical, demographic, and premorbid variables that impact PTS risk after TBI[6;8;9;19]. However, no recent studies have attempted to develop and validate prognostic models for PTS based on identified risk factors. Based on this information and our hypotheses regarding the relevance of variables collected in the TBIMS, we developed prognostic models for PTS during acute hospitalization, at Year-1, and Year-2 following TBI for individuals requiring acute hospitalization and receiving inpatient rehabilitation at designated TBIMS centers. We internally validated these models using resampling techniques and generated discrimination statistics. Within each model, multiple risk factors were significant predictors of PTS. C-statistics demonstrated that models had fair to good ability to discriminate between individuals with and without PTS at Year-1 and Year-2. However, the prognostic model for acute hospitalization did not perform much better than chance for predicting PTS. Nonetheless, variables identified as PTS predictors over time may shed light on vulnerable risk groups and the temporal nature of specific clinical and demographic PTS risk factors.

Previous early PTS studies have not extensively examined demographic characteristics as risk factors. Sex was the only significant demographic PTS predictor (men at increased risk) and only in the acute care model. This finding must be interpreted with caution because of the model's poor discrimination ability. Age, however, has been documented as a risk factor for early (young children at increased risk versus adults[7;19]) and late PTS (among adults, individuals greater than 65 at increased risk). Though we examined age, and it was selected for inclusion in each multivariable model based on bivariate logistic regression, age was not a significant predictor in final multivariable prognostic models. This finding may be attributed to correlation (shared variance) among age and other variables included in final prognostic models such as pre-injury or injury characteristics (SDH, contusion load, limitation in learning/remembering/concentrating) (data not shown). Subsequently, when examined in multivariable models, other predictors may be stronger indicators of PTS risk, therefore excluding age from models.

We identified pre-injury limitation in learning, remembering, or concentrating as a significant PTS predictor during acute hospitalization. This variable may capture latent premorbid neurobiological differences that increase seizure susceptibility, evidenced by increased epilepsy rates among

individuals with developmental disabilities[25]. Pre-injury MH treatment or psychiatric hospitalization was a significant PTS predictor at Year-1. Notably in our analyses, 22% of individuals reported history of MH treatment and/or hospitalization for psychiatric disorder. Existing research indicates bidirectional relationships between psychiatric conditions and epilepsy[26]. These associations may be attributable to common neuropathological mechanisms, such as regional monoaminergic dependent derangements in glutamate management and neurotransmission[26]. Medications for MH disorders including antipsychotics (e.g. chlorprothixene, clozapine) and specific antidepressants (e.g. maprotiline, venlafaxine), may decrease seizure threshold, further increasing seizure risk after TBI[27]. Previous work suggests depression history, common after TBI and prevalent in 21% of the study population, is associated with increased late PTS risk[9;28]. Many individuals take anti-depressants to address clinical symptoms. MH disorders, including depression, may also co-occur with ongoing substance and/or alcohol use problems that may impact PTS risk. History of drug use, alcohol risk, and alcohol documented during acute hospitalization were each examined as predictors of PTS. However, none were significant predictors in multivariable models. Yet, clinicians may need to weigh seizure risk into their selection of antidepressants in this population and screen for substance use disorders when assessing PTS risk. Further studies are needed to evaluate seizure risk among individuals receiving psychotropic medications after TBI.

Pre-injury incarceration was a significant predictor at Year-1 and Year-2. One study reports higher percentages of prior arrest and incarceration among individuals with late PTS versus those without late PTS[29]. Incarceration is associated with increased impulsivity[30] and associated behaviors (e.g. aggression, risk taking, substance use)[31]. These individuals may have underlying neuropathologies involving limbic structures and neurotransmitter disruption in the nucleus accumbens that impact cortical cognitive control[31], predisposing them to risky behaviors that may result in TBI and PTS. Thus, incarceration may represent latent neurobiological traits not otherwise accounted for by data collected. Furthermore, incarceration history may also reflect history of or ongoing substance

and/or EtOH use, as well as developmental disability, psychiatric condition, and history of violence, including previous TBI.

Contrary to expectation, previous moderate/severe TBI did not predict PTS. To our knowledge, no previous study has examined PTS risk after multiple moderate/severe TBI. We hypothesized pathology from prior injury increases PTS risk after subsequent injury. However, the lack of significant findings may be related to low event rates, with less than 3.5% of the population reporting prior moderate/severe TBI. Future work should investigate how multiple TBI affects biosusceptibility to complications like PTS.

Intraparenchymal fragment was a significant PTS predictor at Year-2, consistent with previous research demonstrating higher PTS rates among those with depressed skull fracture[6-8] and pTBI[32]. In our analyses, pTBI was very rare, but also partially defined by the intraparenchymal fragment variable, and was therefore not examined in prognostic models. Injury severity was examined, but not included as a significant PTS predictor at each time point. The lack of predictive ability may be attributed to low sample size or inclusion of other variables associated with injury severity (i.e. intracranial pathologies, craniectomy).

SDH was a significant predictor at Year-1 and Year-2, consistent with previous literature[6;8;20]. SDH was not a significant PTS predictor acutely, but the propensity for temporal glial scarring in SDH regions, and the fundamental role of glial scarring in epileptogenesis[33;34] may explain the temporality of this finding. Contusion load was a significant predictor acutely and at Year-1, and is likely a marker of multifocal injury throughout the brain; contusion has been identified previously as a risk factor for PTS[6; 8; 20]. As contusion load increases, neuronal injury and apoptosis likely increase, disrupting neuronal circuits and predisposing focal areas to ictal discharges. Vascular damage after TBI leads to regional blood extravasation and subsequent generation of blood breakdown products within CNS tissues, perpetuating oxidative stress, another mechanism of epileptogenesis[4;5].

Seizure during acute hospitalization was a significant PTS predictor at Year-1 and Year-2. Although there is debate regarding the “seizure begets seizure” construct[35], research consistently

demonstrates early seizure is associated with increased risk of late PTS[7-9;18]. Immediate/early seizures are considered provoked and non-epileptogenic. However, provoked seizures may exacerbate secondary injury cascades affecting neurochemical and synaptic regulation[36]. Seizures cause reactive astrocytosis and altered glutamate management, further promoting TBI-induced excitoxicity[33]. Reactive astrocytosis also perpetuates the injury-induced inflammatory response, propagating an inflammation/excitation cycle that may result in subsequent seizures[33]. Thus, early seizures, and associated disruptions in critical neuroregulatory mechanisms after injury, may alter neuronal homeostasis, further causing maladaptive neuronal circuit reorganization (plasticity) in what are already seizure-prone systems[37]. While acute hospitalization for the TBIMS population often extends beyond the first week post-TBI, the finding that these seizures contribute to longer term PTE risk underscores the critical need for effective PTS prophylaxis and revisiting if/how current guidelines for medication and treatment duration prevent immediate/early PTS effectively and reduce PTE risk[38].

Craniotomy and craniectomy are common procedures following severe TBI. Recently, decompressive craniectomy (DC) has become a widely used procedure for management of intractable intracranial pressure. Cranial surgeries were among the strongest and most statistically significant PTS predictors in our models, confirming previously published findings[8;20]. However, cranial surgery type reaching statistical significance within models varied across time. We hypothesize this association may stem from both anatomic and physiologic changes from the craniectomy and associated cranioplasty as well as late surgical complications.

Craniotomy and craniectomy are implicated as risk factors for seizure, even when used to address non-traumatic CNS pathologies[39]. Craniectomy carries increased risk for additional brain tissue damage during surgery and secondary to post-operative hematoma and edema[40]. Chronic complications (>1month post-surgery) can occur post-craniectomy, including poor wound healing, infection, and hydrocephalus[40]. Complications and increased morbidity can also occur with subsequent duraplasty/cranioplasty[41]. Thus, delayed pathological mechanisms associated with chronic complications and subsequent cranioplasty may explain the temporality of craniectomy as a significant

PTS predictor. Observational and retrospective studies note more severe injury among individuals undergoing craniectomy versus craniotomy or standard care[42]. Our prognostic models include multiple injury severity and pathology measures, yet craniectomy remained among the strongest predictors, supporting the idea that craniectomy is associated with increased PTS risk, independent of injury severity. PTS prophylaxis guidelines[38] do not reflect trends in neurosurgical intervention for TBI treatment and may benefit from additional research that considers these issues.

Although these are the first prognostic models to reflect current trends in TBI severity, diagnosis, and treatment which elucidate potentially important PTS predictors, there are important limitations to consider. Relative to prognostic studies in general, sample sizes in current analyses were small. Ability to discriminate PTS was poor during acute hospitalization. Low acute model performance may be due to the fact that seizure status during acute hospitalization does not differentiate between immediate, early, and late seizures. As a result, this study could not address the prediction of PTE during acute hospitalization per se. Differentiating between these time points as outcomes could improve individual model performance as PTS risk factors temporally evolve. Alternatively, factors predicting acute seizures may be so diverse that prognostic models would not be effective. Acute seizures may include those detected via electroencephalogram (EEG). However, we do not know if EEG was used to capture seizure activity, if specific individuals only were monitored using continuous EEG, or if EEG monitoring/screening practices differed across TBIMS centers.

Misclassification of PTS status during acute hospitalization from ICD-9 codes, the inability to determine premorbid seizure/epilepsy disorder, and Year-1/Year-2 PTS misclassification also limit model performance. Importantly, PTS status misclassification at Year-1 and Year-2 due to reliance on self-report can occur due to psychogenic seizure reporting or misreporting due to recall bias. However, for large epidemiological studies, it is not always feasible to determine PTS status through in-depth neurological examination or medical record review. Therefore, self-report remains a common practice for seizure/epilepsy[43] and other types of epidemiological research. Multiple sources of misclassification

bias may significantly impact effect size estimations, under- or overestimating the effect of predictors of interest, according to the predictors association with the cause of misclassification.

Lack of information on medication use prohibited investigating how psychotropics affect PTS risk. Therefore, we cannot determine if inclusion of MH disorder/psychiatric hospitalization is predictive or if this variable represents increased PTS risk secondary to psychotropic medication use. We were also unable to control for AED effects on acute hospitalization or Year-1/Year-2 seizure risk, including differential effects of specific medication type. However, in a single TBIMS center, 96% of individuals with severe TBI received seizure prophylaxis during acute care[44]. It is possible, but cannot be confirmed, other TBIMS centers would have similar prophylaxis rates. Additionally, the TBIMS-ND includes only individuals surviving acute injuries and receiving acute inpatient rehabilitation after moderate-severe TBI. Results here may not extrapolate to all individuals with moderate-severe TBI. Lastly, the observational design does not provide causal evidence among relationships with PTS outcome.

Despite limitations, these prognostic models may have added benefit versus prior models, which were not used clinically even though they were reliable in multiple study populations[14;16]. Previous models focused on calculating PTS probability or seizure recurrence over time[14-16], while our prognostic models reflect current trends in TBI diagnosis, treatment, and population characteristics, and investigate multiple risk factors identified in previous PTS studies. Regardless, these models must be examined in independent study populations to determine discriminability and validity outside the TBIMS population. Individuals with characteristics identified in prognostic models as predictors of PTS represent subpopulations that may benefit from tailored seizure prophylaxis guidelines addressing unique premorbid characteristics, pathologies, and procedures.

Further study is required to determine whether new evidence of biological PTS risk factors improves the clinical utility of prognostic models. Year-1 and Year-2 models had optimism-corrected C-statistics greater than 0.70 (0.747, 0.716, respectively). While these values indicate good discriminatory ability, there remains room for improvement. Moderating factors, including those occurring after the

index TBI (e.g. ongoing EtOH and substance use, recurrent TBI) may influence the predictive capacity of our current models. Of particular interest are genetic factors previously shown to be associated with accelerated epileptogenesis and seizure risk after TBI[44;45]. These studies suggest genetic variation remains a significant PTS risk factor after controlling for other factors including injury severity and SDH. Data regarding genetic variation in epileptogenic pathways could improve prognostic ability for PTS, much the way genetic information improved breast cancer prognostication[46]. As modern medical and prevention efforts for PTS move toward personalized medicine approaches, personal biology metrics like genetic variation and inflammation may contribute meaningfully to prognostication and treatment development.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. No authors have any conflict of interest.

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Key Points

1. Prognostic models at Years 1 and 2 post-TBI performed well at discriminating between individuals who did and did not develop PTS
2. Developed models reflect current trends in TBI severity, diagnosis, and treatment
3. Neurosurgical procedures were among the strongest predictors of PTS in each model
4. Pre-injury personal and medical history variables were included as significant predictors of PTS at each time-point

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Figure Legends

Figure 1. Histogram depicting predictors of interest included in prognostic models of PTS during acute care hospitalization (blue), at Year-1 (red), and Year-2 (green) post-injury. Y-axis represents the percent of bootstrap models the predictor of interest was retained in after backward stepwise elimination. Variables without a column for a specific time-point were not considered as a predictor of interest for the time-point. PTA=post-traumatic amnesia; SDH=subdural hematoma; SAH=subarachnoid hemorrhage; EDH=epidural hematoma; SCI=associated spinal cord injury; MH=mental health; Psych Hosp=psychiatric hospitalization.

Supplemental Figure 1. Consort like diagram depicting the flow of individuals evaluated for development of prognostic models at progressive time-points within the TBIMS-ND.

Table 1. Risk Factors Selected for Consideration in Prognostic Models

	Variable	Definition	Method
Demo-graphics	Sex	Biological sex	
	Age	Age at Injury	
	Race	Self-identified race [white, black, other (including Asian/Pacific Islander, Native American, Hispanic Origin, Other, Race unspecified)	SR
Personal and Medical History	Previous TBI	From Ohio State University (OSU) TBI Identifier; number of any TBI prior to index injury	SR
	Previous Moderate/Severe TBI	From OSU TBI identifier; moderate or severe TBI prior to index injury	SR
	Previous TBI with loss of consciousness	From OSU TBI ID; TBI with loss of consciousness prior to index injury	SR
	Alcohol Risk	Adapted from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) categories of risk of alcohol use (safe, at risk, heavy); based on self-reported frequency of drinks and binge drinking episodes	CV
	Preinjury Drug Use	In the year prior to index injury, did the participant use any illicit or non-prescription drugs	SR
	Condition Significantly Limiting Physical Activity	A condition that substantially limits one or more basic physical activities such as walking, climbing stairs, reaching, lifting, or carrying prior to injury	SR
	Limitation in Learning, Remembering, Concentrating	Difficulty in learning, remembering, or concentrating due to a physical, mental, or emotional condition that has been present for at least 6 months prior to injury	SR
	Treatment for Mental Health Condition	Treatment for any mental health problems prior to injury (e.g. depression, anxiety, schizophrenia, and alcohol & drug abuse)	SR
	Psychiatric Hospitalization	Any psychiatric hospitalization prior to injury	SR
	Suicide Attempt	Suicide attempt prior to injury	SR
	Incarceration	Any penal incarcerations with conviction for felony prior to injury	SR
	Military Service	Any military service prior to injury	SR
	Military Combat	Deployed to a combat zone prior to injury	SR
Injury Characteristics	Injury Severity	**Moderate**: normal or abnormal imaging with 30min < LOC < 24 hours, or 1day<PTA<7days, or GCS 9-12 **Severe**: normal or abnormal imaging with -->LOC >24 hours, or PTA>7days, or GCS 3-8	MRR
	Acute Alcohol	Alcohol abuse, dependence, or withdrawal related ICD-9 code documented during acute hospitalization	MRR
	Post Traumatic Amnesia (PTA)	Days of post-traumatic amnesia	MRR
	Loss of Consciousness (LOC)	Duration of loss of consciousness	MRR
	Subdural Hematoma (SDH)	Presence of extra-axial collection within subdural space including hematoma and hygroma	MRR
	Subarachnoid Hemorrhage (SAH)	Blood in ambient, basal, interpeduncular cisterns or cisterna magna, or along falx or tentorium	MRR
	Intra-ventricular Hemorrhage (IVH)	Blood documented within intra-ventricular space	MRR

	Epidural Hematoma (EDH)	Presence of extra-axial collection within epidural space	MRR
	Contusion Load	Calculated by summing the number of regions with parenchymal contusions documented in medical record. Regions were specified by cortical area or non-cortical focal contusion. A maximum of 6 regions were documented (frontal, temporal, parietal, occipital, focal non-cortical, not specified)	CV
	Retained Fragment	Intraparenchymal fragment including fractures displaced >2mm, excluding existing surgical clips or coils	MRR
	Penetrating TBI	Calculated via validated algorithm using imaging reports of retained fragment and mechanism of injury from medical record review.	CV
	Associated Spinal Cord Injury	Injury to neural elements of spinal cord present or absent	MRR
	Seizure during Acute Care Hospitalization	Inclusion of ICD-9 codes 780.39, 780.33, and 345.0x → 345.9x within first 20 ICD-9 codes reported during acute care hospitalization	MRR
Surgical Pro-cedures	Craniotomy	Surgical procedure, defined as "cranium opened, something removed, cranium closed"	MRR
	Craniectomy	Surgical procedure, define as "cranium opened and left open"	MRR

Method abbreviations: MRR: medical record review; CV: calculated value; SR: self-report
Variable Abbreviations: GCS: Glasgow Coma Scale; LOC: Loss of Consciousness; PTA: Post-traumatic Amnesia; ICD: International Classification of Disease;

Table 2: Population Characteristics, N(%)

			Acute	Year 1	Year 2
Sample Size			2136	2079	1364
Post-Traumatic Seizure			187 (8.8)	210 (10.1)	139 (10.2)
		Incident Seizure^	187 (8.8)	173 (82.4)	53 (38.1)
		Recurrent Seizure^	---	37 (17.6)	85 (61.2)
Multiple Seizures since last Follow-up^			---	123 (58.6)	88 (63.3)
Age at Injury*			44.7 (20.1)	44.7 (20.1)	43.9 (19.9)
Sex	Male		1569 (73.5)	1526 (73.4)	1009 (74.0)
	Female		566 (25.5)	552 (26.6)	355 (26.0)
Race	White		1446 (67.7)	1402 (67.5)	935 (68.6)
	Black		301 (14.1)	293 (14.1)	197 (14.4)
	Other		388 (18.2)	383 (18.4)	232 (17.0)
Pre-injury Drug Use			379 (17.8)	368 (17.7)	243 (17.8)
Pre-injury Alcohol Risk		Low Use	1458 (68.3)	1422 (68.3)	918 (67.3)
		At Risk	596 (27.9)	578 (27.8)	396 (29.0)
		Heavy Use	81 (3.8)	78 (3.8)	50 (3.7)
Pre-injury Incarceration			194 (9.1)	191 (9.2)	129 (9.5)
Injury Severity	Moderate		448 (21.0)	435 (20.9)	271 (19.9)
	Severe		1688 (79.0)	1644 (79.1)	1093 (80.1)
Mechanism of Injury	Motorized vehicle		956 (44.8)	925 (44.5)	640 (46.9)
	Violence		179 (8.4)	176 (8.5)	117 (8.6)
	Sport		129 (6.0)	125 (6.0)	81 (5.9)
	Fall		685 (32.1)	669 (32.2)	396 (29.0)
	Hit by Object		29 (1.4)	28 (1.4)	16 (1.2)
	Pedestrian Struck		144 (6.7)	142 (6.8)	107 (7.8)
	Other		14 (0.7)	14 (0.7)	7 (0.5)
Post Traumatic Amnesia (Days)*			30.1 (37.3)	30.1 (37.2)	30.2 (38.2)
Length of Acute Stay (Days)*			21.5 (20.6)	21.5 (20.6)	21.9 (21.8)
Intraparenchymal Fragment			127 (5.9)	121 (5.8)	84 (6.2)
Subdural Hematoma			1124 (52.6)	1093 (52.6)	727 (53.3)
Craniotomy			336 (15.7)	326 (15.7)	222 (16.3)
Craniectomy			296 (13.9)	288 (13.9)	187 (13.7)
Acute Alcohol			541 (25.3)	525 (25.3)	345 (25.3)

^of individuals with evidence of seizure activity at time-point

**mean(SD)*

Table 3. Final Prognostic Model and Fit Statistics for Prediction of PTS

Model	Number Bootstrap Samples	C Statistics			Final Prognostic Model for PTS
		Saturated Model	Training Model[1]	Final Model[2]	
Acute	999	0.638	0.661	0.599	PTS Acute Hospitalization = -3.81 + 0.47*Sex + 0.78*PreInjury Limitation Learning, Remembering, Concentrating + 0.70*Contusion Load 1 + 0.61*Contusion Load 2 + 0.73*Contusion Load 3 + 0.62*Contusion Load 4 + 0.63*Craniotomy
Year 1	984	0.772	0.787	0.747	PTS Year 1 = -3.86 + 0.22*PreInjury Mental Health Treatment + 0.49*PreInjury Mental Health Treatment and Psychiatric Hospitalization + 1.78*PreInjury Psychiatric Hospitalization + 1.02*PreInjury Incarceration + 0.005*Post-Traumatic Amnesia + 0.54*Subdural Hematoma + 0.76*Contusion Load 1 + 0.75*Contusion Load 2 + 0.66*Contusion Load 3 + 0.54*Contusion Load 4 + 0.75*Seizure Acute Hospitalization + 0.62*Craniotomy + 1.29*Craniectomy
Year 2	1000	0.758	0.789	0.716	PTS Year 2 = -3.23 + 0.76*PreInjury Incarceration + 0.83*Subdural hematoma + 0.80*Retained Fragment + 1.27*Seizure Acute Hospitalization + 0.49*Craniotomy + 1.00*Craniectomy

[1] Bootstrapped model
[2] Optimism corrected

Table 4. Variables Included for Prognostic Model to Predict PTS at Year 1

Variable*	Retained in Reduced Model	Adjusted Odds Ratio	P-value
Sex (ref=female)	No	---	---
Age	No	---	---
Previous Moderate or Severe TBI	No	---	---
Pre-injury Treatment for mental health condition/Psychiatric hospitalization (ref=neither)	**Yes**	---	---
Treatment, no hospitalization		**1.25**	**0.30**
Treatment and Hospitalization		**1.63**	**0.103**
Hospitalization		**5.96**	**0.004**
Pre-injury Drug Use	No	---	---
Pre-injury Alcohol Risk	No	---	---
Pre-injury Suicide Attempt	No	---	---
Pre-injury Incarceration	**Yes**	**2.78**	**<0.001**
Pre-injury Military Service	No	---	---
Injury Severity	No	---	---
Acute Alcohol	No	---	---
Duration PTA (days)	**Yes**	**1.01**	**0.011**
Length of Acute Stay	No	---	---
Subdural Hematoma	**Yes**	**1.72**	**0.003**
Subarachnoid Hemorrhage	No	---	---
Epidural Hematoma	No	---	---
Contusion Load (ref=0)	**Yes**		
1		**2.14**	**0.001**
2		**2.11**	**0.001**
3		**1.93**	**0.018**
4		**1.71**	**0.097**
Retained Fragment	No	---	---
Seizure during Acute Hospitalization	**Yes**	**2.12**	**0.001**
Craniotomy	**Yes**	**1.86**	**0.001**
Craniectomy	**Yes**	**3.64**	**<0.001**

**Variables included in saturated logistic regression model*
Unless noted, reference group for adjust odds ratio is variable not present
TBI: Traumatic Brain Injury; PTA: Post-traumatic Amnesia

Table 5. Variables Included for Prognostic Model to Predict PTS at Year 2

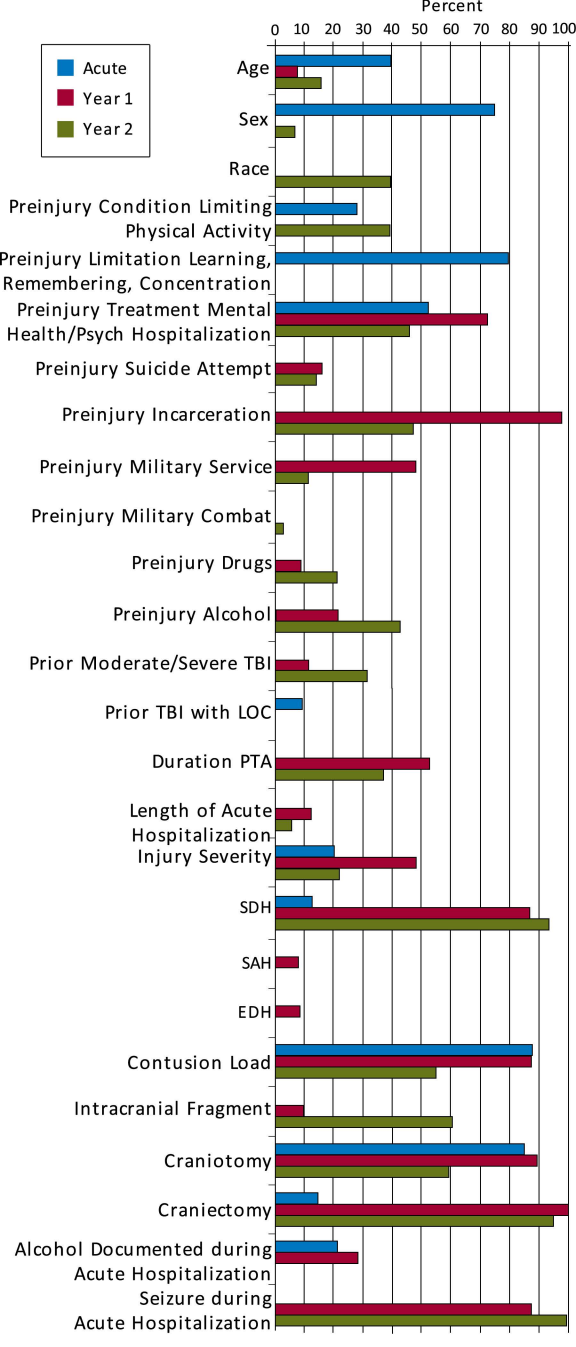
Variable*	Retained in Reduced Model	Adjusted Odds Ratio	P-value
Sex (ref=female)	No	---	---
Age	No	---	---
Race	No	---	---
Previous Moderate or Severe TBI	No	---	---
Pre-injury Alcohol Risk	No	---	---
Pre-Injury Condition Limiting Physical Activity	No	---	---
Pre-injury Treatment for mental health condition/Psychiatric hospitalization	No	---	---
Pre-injury Suicide Attempt	No	---	---
Pre-injury Incarceration	**Yes**	**2.14**	**0.009**
Pre-injury Military Service	No	---	---
Pre-injury Military Combat	No	---	---
Injury Severity	No	---	---
Duration PTA	No	---	---
Length of Acute Stay	No	---	---
Subdural Hematoma	**Yes**	**2.29**	**<0.001**
Contusion Load	No	---	---
Retained Fragment	**Yes**	**2.23**	**0.010**
Seizure during Acute Hospitalization	**Yes**	**3.57**	**<0.001**
Craniotomy	**Yes**	**1.64**	**0.036**
Craniectomy	**Yes**	**2.71**	**<0.001**

**Variables included in saturated logistic regression model*
Unless noted, reference group for adjust odds ratio is variable not present
TBI: Traumatic Brain Injury; PTA: Post-traumatic Amnesia

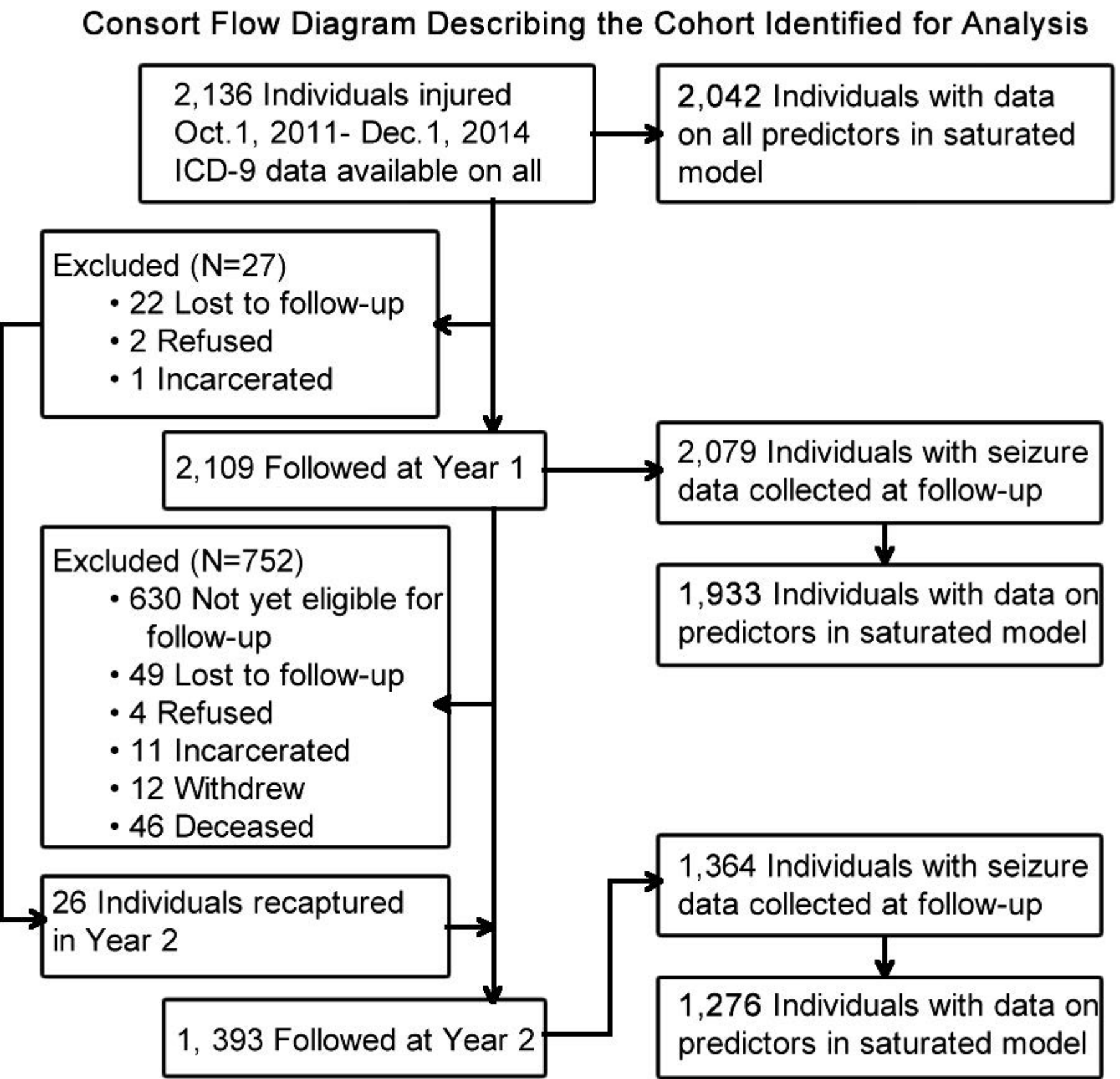
Supplemental Table 1. Variables Included for Prognostic Model to Predict PTS during Acute Care Hospitalization

Variable*	Retained in Reduced Model	Adjusted Odds Ratio	P-value
Sex (ref=female)	**Yes**	**1.60**	**0.022**
Age	No	---	---
Previous TBI with LOC	No	---	---
Pre-Injury Condition Limiting Physical Activity	No	---	---
Pre-Injury Limitation in Learning, Remembering, or Concentrating	**Yes**	**2.18**	**0.001**
Pre-injury Treatment for mental health condition/Psychiatric hospitalization	No	**---**	**---**
Injury Severity	No	---	---
Acute Alcohol	No	---	---
Duration PTA	No	---	---
Length of Acute Stay	No	---	---
Subdural Hematoma	No	---	---
Contusion Load (ref=0)	**Yes**		
1		**2.02**	**0.001**
2		**1.84**	**0.008**
3		**2.08**	**0.006**
4		**1.85**	**0.061**
Retained Fragment	No	---	---
Craniotomy	**Yes**	**1.86**	**0.001**
Craniectomy	No	---	---

**Variables included in saturated logistic regression model*
Unless noted, reference group for adjust odds ratio is variable not present
TBI: Traumatic Brain Injury; LOC: Loss of Consciousness; PTA: Post-Traumatic Amnesia



Histogram Depicting percent of Bootstrapped Samples each Predictor of Interest Selected


Consort Flow Diagram Describing the Cohort Identified for Analysis
2,136 Individuals injured Oct.1, 2011- Dec.1, 2014 ICD-9 data available on all
2,042 Individuals with data on all predictors in saturated model
Excluded (N=27)
• 22 Lost to follow-up
• 2 Refused
• 1 Incarcerated
2,109 Followed at Year 1
2,079 Individuals with seizure data collected at follow-up
1,933 Individuals with data on predictors in saturated model
Excluded (N=752)
• 630 Not yet eligible for follow-up
• 49 Lost to follow-up
• 4 Refused
• 11 Incarcerated
• 12 Withdrew
• 46 Deceased
26 Individuals recaptured in Year 2
1,364 Individuals with seizure data collected at follow-up
1, 393 Followed at Year 2
1,276 Individuals with data on predictors in saturated model