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Prior traumatic brain injury is a risk factor for in-hospital mortality in moderate to severe traumatic brain injury: a TRACK-TBI cohort study

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ABSTRACT

Objectives An estimated 14–23% of patients with traumatic brain injury (TBI) incur multiple lifetime TBIs. The relationship between prior TBI and outcomes in patients with moderate to severe TBI (msTBI) is not well delineated. We examined the associations between prior TBI, in-hospital mortality, and outcomes up to 12 months after injury in a prospective US msTBI cohort.

Methods Data from hospitalized subjects with Glasgow Coma Scale score of 3–12 were extracted from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study (enrollment period: 2014–2019). Prior TBI with amnesia or alteration of consciousness was assessed using the Ohio State University TBI Identification Method. Competing risk regressions adjusting for age, sex, psychiatric history, cranial injury and extracranial injury severity examined the associations between prior TBI and in-hospital mortality, with hospital discharged alive as the competing risk. Adjusted HRs (aHR (95% CI)) were reported. Multivariable logistic regressions assessed the associations between prior TBI, mortality, and unfavorable outcome (Glasgow Outcome Scale-Extended score 1–3 (vs. 4–8)) at 3, 6, and 12 months after injury.

Results Of 405 acute msTBI subjects, 21.5% had prior TBI, which was associated with male sex (87.4% vs. 77.0%, p=0.037) and psychiatric history (34.5% vs. 20.7%, p=0.010). In-hospital mortality was 10.1% (prior TBI: 17.2%, no prior TBI: 8.2%, p=0.025). Competing risk regressions indicated that prior TBI was associated with likelihood of in-hospital mortality (aHR=2.06 (1.01–4.22)), but not with hospital discharged alive. Prior TBI was not associated with mortality or unfavorable outcomes at 3, 6, and 12 months.

Conclusions After acute msTBI, prior TBI history is independently associated with in-hospital mortality but not with mortality or unfavorable outcomes within 12 months after injury. This selective association underscores the importance of collecting standardized prior TBI history data early after acute hospitalization to inform risk stratification. Prospective validation studies are needed.

Level of evidence IV.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The relationship between prior traumatic brain injury (TBI) history, acute recovery, and longitudinal outcomes after moderate to severe TBI (msTBI) is not well characterized.

WHAT THIS STUDY ADDS

⇒ In a prospectively enrolled acute msTBI cohort across 18 US trauma centers, prior TBI with alteration of consciousness or amnesia was associated with greater risk of in-hospital mortality, but not mortality or functional outcomes across 12 months after injury.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underscore the importance of collecting prior TBI history data early during hospitalization after acute msTBI to inform triage and risk stratification.

Trial registration number NCT02119182.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of morbidity worldwide,[1] comprising 15% and 30% of injury-related hospitalizations and deaths in the USA, respectively.[2] Patients who survive moderate to severe TBI (msTBI) are at risk of functional dependence[1 3 4] and often experience persistent physical, cognitive, and behavioral impairments that interfere with return to work and preinjury societal activities.[5 6]

An estimated 14–23% of patients with acute TBI have sustained ≥1 prior TBI.[7–9] Repetitive TBI is associated with postconcussive symptoms (PCS), cognitive dysfunction, and lower life satisfaction, and is a risk factor for mortality in patients with mild TBI.[10] Studies to date have primarily focused on repetitive TBI in sports and mild TBI. Sequelae of patients with msTBI with prior TBI have not

been well characterized. The observational, multicenter TBI Model Systems National Database Study enrolled patients with msTBI requiring hospitalization and subsequent rehabilitation and investigated longitudinal multidomain outcomes. A 2013 TBI Model Systems study of 4464 patients with msTBI found that history of TBI earlier in life was associated with behavioral issues 1–20 years after the subsequent TBI of enrollment into the study, without differences in rehabilitation length of stay (LOS).[8] A 2020 TBI Model Systems study of 5054 patients with msTBI showed that prior msTBI was associated with worse functional independence at 1, 2, and 5 years after injury.[11]

Our study aimed to (1) characterize sociodemographic and clinical differences by prior TBI history and (2) elucidate the relationships among prior TBI, hospital outcomes, and longitudinal outcomes across 12 months after injury in a prospectively enrolled US cohort of patients with msTBI from the 18-center Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study.[12] We hypothesized that prior TBI would be associated with higher risks of in-hospital mortality, as well as mortality and functional disability at 3, 6, and 12 months after injury.

METHODS

Study overview

The observational TRACK-TBI Study (ClinicalTrials.gov NCT02119182) enrolled subjects through convenience sampling between March 2, 2014 and June 22, 2019. The subjects presented to the emergency department (ED) of 1 of 18 US level 1 trauma centers with alteration of consciousness, amnesia or neurological deficit[13] and received a clinically indicated head CT scan within 24 hours of blunt external force head injury. TRACK-TBI Study exclusion criteria were pregnancy, incarceration, psychiatric hold, penetrating TBI, significant polytrauma that could interfere with validity of outcome assessments as determined by the principal investigator at each study site, major/debilitating medical (end-stage malignancy, refractory substance abuse, transmittable disease precluding consent), neurological (cerebrovascular accident, central nervous system (CNS) malignancy, cognitive impairment), or mental health conditions (schizophrenia) that could interfere with validity of outcome assessments, and ongoing participation in an interventional trial (drug, device, behavioral).[14]

For our current retrospective cohort analysis of the prospectively enrolled TRACK-TBI Study sample, data were extracted from hospitalized TRACK-TBI subjects aged ≥17 years with available prior TBI information and acute hospital discharge data; msTBI was defined by ED arrival Glasgow Coma Scale (GCS) score of 3–12 (figure 1).

Ethics approval

The Galveston Orientation and Amnesia Test was administered to determine competency for informed consent (passing score=76–100).[15] Subjects without passing scores underwent informed consent by legally authorized representatives (LAR), and competency screening was repeated at each follow-up visit to agree for continued participation.

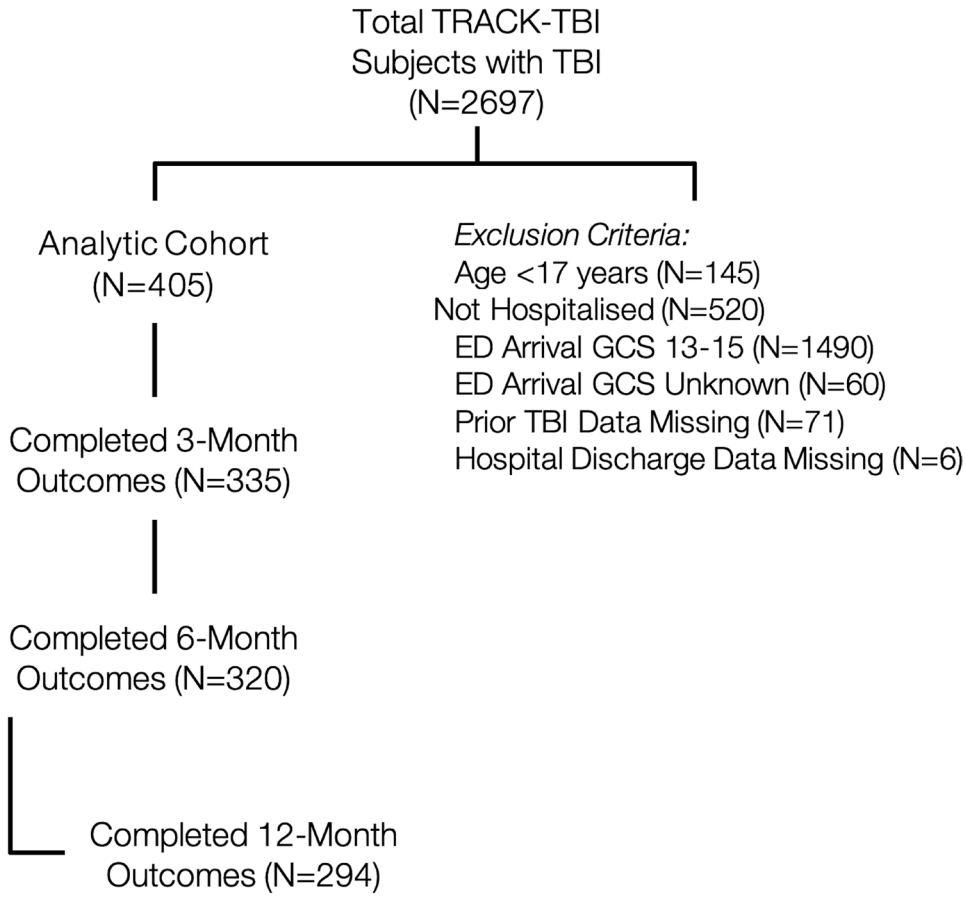

Figure 1 Flow diagram of included subjects from the TRACK-TBI Study. Moderate to severe traumatic brain injury (TBI) was defined as emergency department (ED) arrival Glasgow Coma Scale (GCS) score of 3–12. GCS=Glasgow Coma Scale; TBI=traumatic brain injury; TRACK-TBI=, Transforming Research and Clinical Knowledge in Traumatic Brain Injury.

Table 1 Sociodemographic and clinical characteristics by prior TBI history status

Variable	Prior TBI: No (n=318)	Prior TBI: Yes (n=87)	Significance (P value)
Sociodemographic factors			
Age	n=318	n=87	0.74
Years, mean (SD)	39.0 (16.7)	38.6 (17.2)	
Sex	n=318	n=87	
Male	245 (77.0%)	76 (87.4%)	0.037
Female	73 (23.0%)	11 (12.6%)	
Race/ethnicity*	n=318	n=87	
Non-Hispanic white	187 (58.8%)	53 (60.9%)	0.67
Black	48 (15.1%)	10 (11.5%)	
Hispanic	63 (19.8%)	16 (18.4%)	
Other†	20 (6.3%)	8 (9.2%)	
Education years	n=318	n=87	
Mean (SD)	12.7 (2.7)	12.6 (2.6)	0.86
Insurance	n=311	n=84	
Uninsured	81 (26.1%)	18 (21.4%)	0.83
Private	164 (52.7%)	46 (54.8%)	
Medicare	18 (5.8%)	4 (4.8%)	
Medicaid	43 (13.8%)	14 (16.7%)	
Other	5 (1.6%)	2 (2.4%)	
Unemployed	n=316	n=86	
No	290 (91.8%)	76 (88.4%)	0.39
Yes	26 (8.2%)	10 (11.6%)	
Psychiatric history	n=318	n=87	
No	252 (79.3%)	57 (65.5%)	0.01
Yes	66 (20.7%)	30 (34.5%)	
Tobacco use	n=238	n=67	
No	145 (60.9%)	42 (62.7%)	0.88
Yes	93 (39.1%)	25 (37.3%)	
Alcohol abuse	n=284	n=77	
No	152 (53.5%)	43 (55.8%)	0.80
Yes	132 (46.5%)	34 (44.2%)	
Drug use	n=274	n=78	
No	195 (71.2%)	50 (64.1%)	0.26
Yes	79 (28.8%)	28 (35.9%)	
Drug trouble	n=268	n=77	
No	249 (92.9%)	65 (84.4%)	0.039
Yes	19 (7.1%)	12 (15.6%)	
Clinical injury factors			
GCS at ED arrival	n=318	n=87	
Median (IQR)	4 (3–8)	5 (3–9)	0.61
Extracranial ISS	n=314	n=82	
Median (IQR)	4 (1–13)	4 (1–10)	0.64
AIS by body region, median (IQR)	n=314	n=82	
Head or neck	4 (3–5)	4 (3–5)	0.95
Face	0 (0–2)	1 (0–2)	0.19
Chest	0 (0–2)	0 (0–2)	0.86
Abdomen or pelvic contents	0 (0–0)	0 (0–0)	0.17
Extremities or pelvic girdle	0 (0–2)	0 (0–2)	0.20
External	1 (0–1)	1 (0–1)	0.005
Cause of injury	n=316	n=86	
Road traffic collision	194 (61.4%)	46 (53.5%)	0.16
Incidental fall	74 (23.4%)	18 (20.9%)	
Violence/assault	20 (6.3%)	9 (10.5%)	
Other	28 (8.9%)	13 (15.1%)	
Marshall CT score	n=295	n=81	
1	28 (9.5%)	10 (12.4%)	0.88
2	135 (45.8%)	37 (45.7%)	
3–4	26 (8.8%)	7 (8.6%)	
5–6	106 (35.9%)	27 (33.3%)	
Cranial surgery/ICP monitor	n=318	n=87	
No	110 (34.6%)	40 (46.0%)	0.06
Yes	208 (65.4%)	47 (54.0%)	
In-hospital cause of death‡	n=26	n=15	
TBI/initial injury	21 (80.8%)	10 (66.8%)	0.37
TBI/secondary ICH	2 (7.7%)	4 (26.7%)	
Medical complications	1 (3.8%)	1 (6.7%)	
Systemic trauma	2 (7.7%)	0 (0%)	

Sociodemographic and clinical factors compared by prior TBI status. The sample sizes with complete data for each variable were provided in rows with the variable name.
*Race and ethnicity were obtained through self-report and medical record review.
†The 'Other' race category included Asian, Alaskan Native, Inuit, Indian, Native American and Pacific Islander.
‡Cause of death was available for patients who died in hospital (prior TBI=no, n=26; prior TBI=yes, n=15).
AIS, Abbreviated Injury Scale; ED, emergency department; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; ICP, intracranial pressure; ISS, Injury Severity Score; TBI, traumatic brain injury.

Prior TBI history

The Ohio State University TBI Identification Method (OSU-TBI-ID) has been extensively validated for the assessment of prior TBI history[16 17] and was obtained from subjects or their LAR on enrollment into the TRACK-TBI Study. In our study, prior TBI was defined as TBI with alteration of consciousness or amnesia *prior* to the index TBI of enrollment into the TRACK-TBI Study.

Sociodemographic and clinical variables

Sociodemographic (age, sex, race/ethnicity, education, insurance), medical history by body system, acute injury and hospital course variables were collected through patient interview and medical record review. History of psychiatric disorder was defined as a pre-existing disorder diagnosed by a medical professional. Prior alcohol, tobacco, and drug history within 12 months prior to current injury was collected using the Alcohol Use Disorders Identification Test.[18] 'Drug Trouble' was defined as endorsing 'Yes' to 'Have you ever been in trouble at school, work, or with relationships because of drug use?' Acute injury variables included mechanism, GCS, Marshall CT Classification score,[19] extracranial Injury Severity Score (ISS),[20] Abbreviated Injury Scale (AIS) scores by body system,[21] cranial surgery, intracranial pressure (ICP) monitor, and in-hospital cause of death.

Acute hospital outcomes

Acute hospital outcomes included in-hospital mortality, hospital LOS (HLOS; days), and hospital discharge disposition. Multivariable competing risk regression models were used to examine the risks associated with prior TBI status for in-hospital mortality/discharged alive as competing events over the duration of acute hospitalization (HLOS). Analytic methodology is provided under the 'Statistical Analysis' section.

Longitudinal outcomes

The Glasgow Outcome Scale-Extended (GOSE) was used to assess functional disability due to TBI at 3, 6, and 12 months and

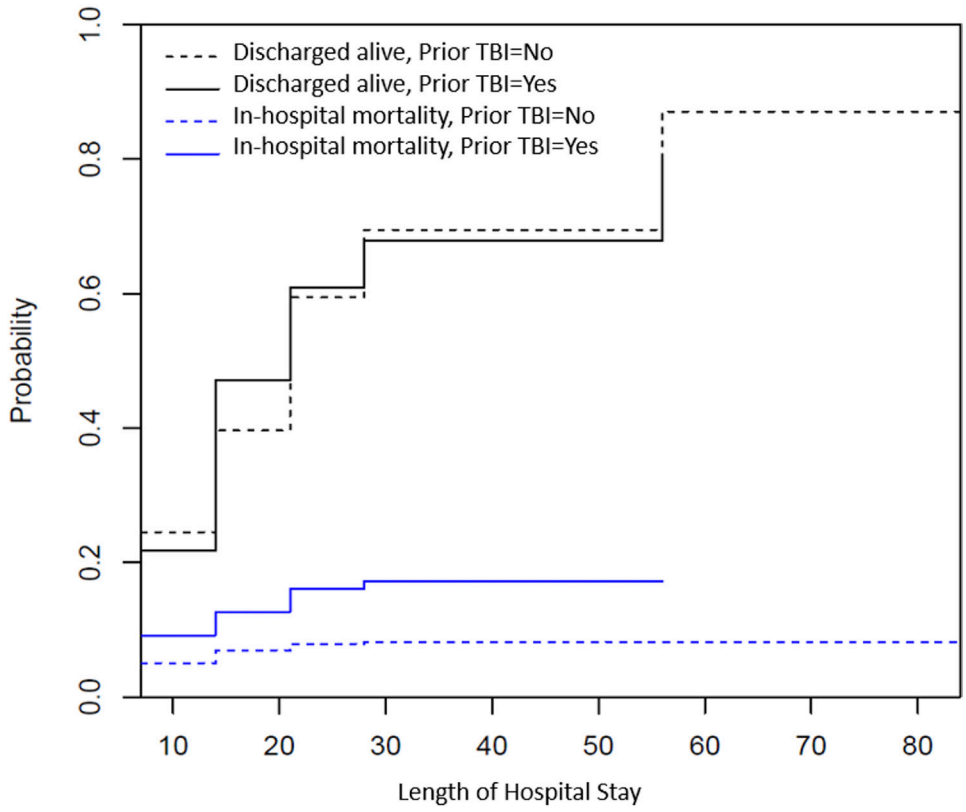

Figure 2 Estimated cumulative incidence function curves for in-hospital mortality and hospital discharged alive over a given hospital length of stay timeframe for patients with versus without prior traumatic brain injury (TBI) history.

was administered by structured interview with patient participants or informants.[22 23] Scoring in this 8-point ordinal measure consists of 1=dead, 2=vegetative state, 3=lower severe disability (can perform activities of daily living (ADL) independently for 0–8 h/day), 4=upper severe disability (can perform ADLs for 8–24 h/day), 5=lower moderate disability (inability to work or to resume preinjury social activities), 6=upper moderate disability (reduced work capacity, >50% reduced social participation, or weekly psychological disturbance), 7=lower good recovery (PCS, <50% reduced social participation, or occasional psychological disturbance), and 8=upper good recovery (return to preinjury functional status). Outcome was defined as unfavorable (GOSE score=1–3) or favorable (GOSE score=4–8) in accordance with recent literature from large multicenter TBI studies.[3 24] Subjects with completed GOSE scores were analyzed at each respective timepoint. Multivariable logistic regression models were used to examine prior TBI as a predictor of 3, 6, and 12-month mortality and unfavorable outcomes. Analytic methodology is provided under the 'Statistical Analysis' section.

Statistical analysis

Sociodemographics, clinical and injury characteristics, and medical histories were compared between subjects with and without prior TBI using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

Competing risk regression analysis was used to simultaneously estimate the probability of in-hospital mortality and hospital discharged alive as two competing events during acute hospitalization, because the occurrence of one event hinders the occurrence of the competing event.[25] The outcome variable in our competing risk models was time from injury to in-hospital death/hospital discharged alive, similar to a survival analysis. Competing risk models have been used in rigorous clinical studies to evaluate the time from major injury and illness to a binary hospital outcome (mortality and discharged alive) to show that predictors may have different associations with HLOS between survivors and non-survivors within a single hospital stay.[26–28] Cumulative incidence functions (CIFs) estimating the joint probability of in-hospital mortality or discharged alive at a given time during hospitalization (HLOS) were plotted with Gray's test for equality of CIFs[25] for subjects with and without prior TBI. Treating mortality/discharged alive as competing risks provides a mechanism to view the CIFs of simultaneous outcomes and enables between-group comparisons of multiple outcome events across a time function. During acute hospitalization for major injury or illness, conventional Kaplan-Meier models have been found to overestimate cumulative incidences compared with competing risk models.[29 30]

Multivariable competing risk regression models[25] assessed the association of prior TBI with in-hospital mortality or discharged alive adjusting for age, sex, psychiatric history (yes vs. no), GCS score (3–8 vs. 9–12), Marshall CT score (3–4 or 5–6 vs. 1–2), polytrauma (extracranial ISS 10–16 or ≥17 vs. ≤9), and cranial surgery or ICP monitor (yes vs. no). The models estimated the association of prior TBI and other covariates with the subdistribution of a particular type of failure in a competing risk setting, with different adjusted HRs (aHR), 95% CIs, and p values for the two competing events. To reduce confounding by prolonged pathways to hospital disposition that may be unrelated to the acute TBI,[31–35] we performed a sensitivity analysis censoring subjects with unfavorable discharge (long-term acute care, nursing facility, nursing home, hospice, or transfer to another hospital), to focus on subjects with in-hospital mortality or discharge to

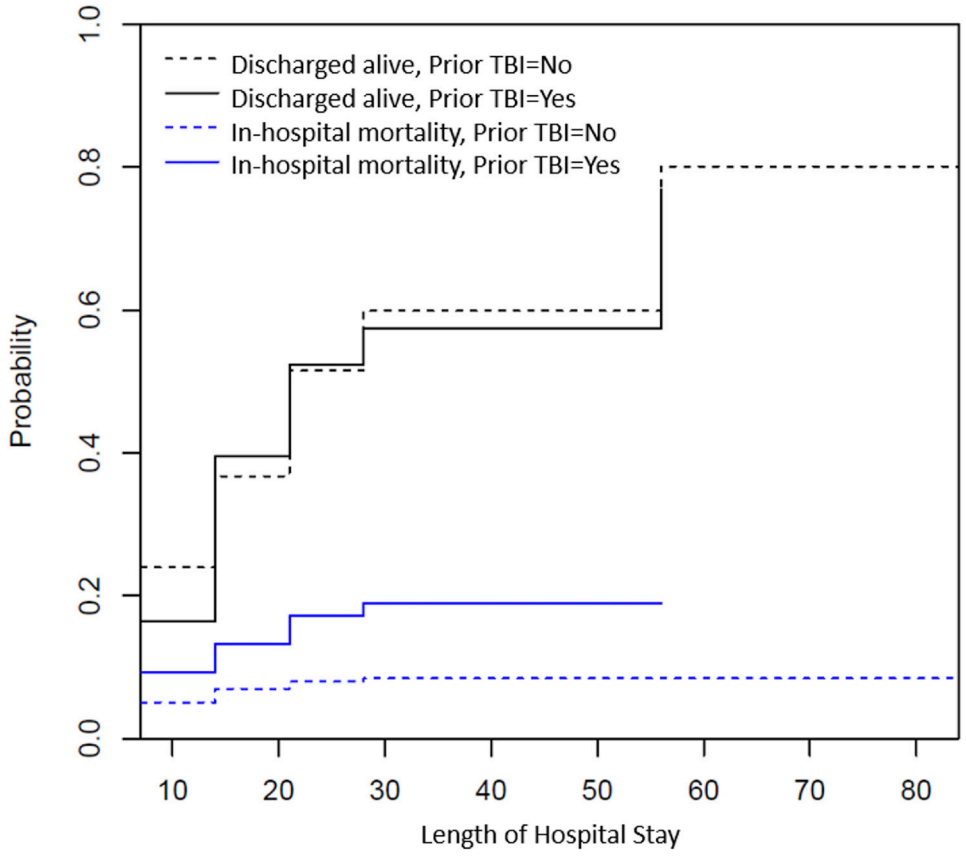

Figure 3 Estimated cumulative incidence function curves for in-hospital mortality and hospital discharged alive over a given hospital length of stay timeframe for patients with versus without prior traumatic brain injury (TBI) history, censoring patients with unfavorable hospital discharge (defined as nursing facility/nursing home, long-term acute care facility, hospice, and transfer to another hospital).

favorable outcome (home or rehabilitation facility). This sensitivity analysis applied the competing risk model to a three-level response variable (0=censor, 1=discharged alive, 2=in-hospital mortality).

Multivariable logistic regression models were used to evaluate the associations of prior TBI with mortality and unfavorable outcomes at 3, 6, and 12 months adjusting for age, sex, psychiatric history, GCS, Marshall CT score, polytrauma, and cranial surgery or ICP monitor. Adjusted ORs (aOR) and 95% CI were reported.

Statistical analyses were performed using R V.4.1.2. The 'cmprsk' and 'crr' packages were used for the competing risk analysis. A two-sided significance threshold of $p<0.05$ was used for all analyses. P values were reported with three decimal points if <0.05 and with two decimal points if ≥0.05.

RESULTS

Overview of analytic cohort

Of the 2697 patients enrolled in the TRACK-TBI Study, 482 were hospitalized for msTBI (ED arrival GCS score 3–12), of which 405 had complete prior TBI and hospital discharge data; this comprised our analytic cohort. Comparison of the included study sample (GCS score 3–12, hospitalized with prior TBI data) versus those without prior TBI data is shown in online supplemental table 1.

In our analytic cohort, 21.5% (87 of 405) had prior TBI. Subjects with prior TBI were more often male (87.4% vs. 77.0%, p=0.037), had baseline psychiatric disorder (34.5% vs. 20.8%, p=0.01), and had history of substance use (15.6% vs. 7.1%, p=0.039) (table 1). No statistically significant differences were observed for age (prior TBI yes vs. no; mean±SD: 38.6±17.2 vs. 39.0±16.7 years, p=0.74), race (non-Hispanic white; 60.9% vs. 58.8%, p=0.67), years of education (mean±SD: 12.6±2.6 vs. 12.7±2.7 years, p=0.86), or baseline medical conditions across cardiac, endocrine, gastrointestinal, hematologic, hepatic, oncologic, pulmonary, and renal systems (data not shown). For acute injury factors, ED arrival GCS score (median (IQR): 5 (3–9) vs. 4 (3–8), p=0.61), Marshall CT score (1, 2, 3–4, 5–6: 12.4%, 45.7%, 8.6%, 33.3% vs. 9.5%, 45.8%, 8.8%, 35.9%, p=0.88) and extracranial ISS (median (IQR): 4 (1–10) vs. 4 (1–13), p=0.64) were comparable between subjects with and without prior TBI (table 1). AIS scores across the six body regions were comparable between prior TBI subgroups, with a statistically but not a clinically significant difference in the AIS-External score (median (IQR): 1 (0–1) for both groups, p=0.005, assessed by the Wilcoxon rank-sum test). A non-significant statistical trend for lower incidence of cranial surgery/ICP monitor was observed for those with prior TBI (54.0% vs. 65.4%, p=0.06) (table 1). No significant differences in the distribution of in-hospital cause of death were observed between prior TBI subgroups (table 1).

Acute hospital outcomes

Overall, in-hospital mortality was 10.1%. Subjects with prior TBI had higher incidence of in-hospital mortality (17.2% vs. 8.2%, p=0.025). In those with in-hospital mortality, median HLOS was 3.8 days (2.7–14.4) for prior TBI versus 5.8 days (3.2–9.3) for no prior TBI. In those discharged alive, median HLOS was 11.4 days (6.7–21.7) for prior TBI versus 15.8 days

Table 2 Competing risk regression model for in-hospital mortality and hospital discharged alive

Variable	Adjusted HR (95% CI)	Significance (P value)
In-hospital mortality		
Prior TBI=yes (vs. no)	2.06 (1.01 to 4.22)	0.049
Age (per year)	1.06 (1.03 to 1.08)	<0.001
Sex=female (vs. male)	0.77 (0.28 to 2.12)	0.61
GCS score 3–8 (vs. GCS score 9–12)	2.78 (1.00 to 7.76)	0.05
Extracranial ISS=10–16 (vs. 0–9)	0.83 (0.33 to 2.08)	0.69
Extracranial ISS>17 (vs. 0–9)	1.12 (0.35 to 3.60)	0.85
Marshall CT 3–4 (vs. 1–2)	8.15 (1.72 to 38.7)	0.008
Marshall CT 5–6 (vs. 1–2)	12.8 (2.02 to 80.6)	0.007
Psychiatric=yes (vs. no)	1.92 (0.90 to 4.10)	0.09
Cranial surgery/ICP monitor=yes (vs. no)	0.68 (0.11 to 4.10)	0.67
Hospital discharged alive		
Prior TBI=yes (vs. no)	0.85 (0.63 to 1.16)	0.30
Age (per year)	0.98 (0.97 to 0.98)	<0.001
Sex=female (vs. male)	0.90 (0.67 to 1.23)	0.52
GCS score 3–8 (vs. GCS score 9–12)	0.63 (0.47 to 0.84)	0.002
Extracranial ISS=10–16 (vs. 0–9)	1.12 (0.76 to 1.63)	0.57
Extracranial ISS>17 (vs. 0–9)	0.54 (0.41 to 0.72)	<0.001
Marshall CT 3–4 (vs. 1–2)	0.79 (0.53 to 1.7)	0.24
Marshall CT 5–6 (vs. 1–2)	0.63 (0.48 to 0.83)	0.001
Psychiatric=yes (vs. no)	0.78 (0.58 to 1.07)	0.12
Cranial surgery/ICP monitor=yes (vs. no)	0.39 (0.29 to 0.52)	<0.001

Multivariable competing risk regression models were used to estimate the association of prior TBI with in-hospital mortality or hospital discharged alive over the length of hospital stay, adjusted for age, sex, psychiatric history (yes vs. no), emergency department (ED) arrival GCS score (3–8 vs. 9–12), Marshall CT score (3–4, 5–6, vs. 1–2), extracranial ISS (10–16, ≥17 vs. 0–9), and cranial surgery/ICP monitor (yes vs. no).
GCS, Glasgow Coma Scale; ICP, intracranial pressure; ISS, Injury Severity Score; TBI, traumatic brain injury.

Table 3 Competing risk regression for in-hospital mortality and hospital discharged alive, censoring for unfavorable hospital discharge

Variable	Adjusted HR (95% CI)	Significance (P value)
In-hospital mortality		
Prior TBI=yes (vs. no)	2.13 (1.04 to 4.37)	0.04
Age (per year)	1.06 (1.03 to 1.08)	<0.001
Sex=female (vs. male)	0.85 (0.33 to 2.23)	0.75
GCS score 3–8 (vs. GCS score 9–12)	2.58 (0.92 to 7.22)	0.07
Extracranial ISS=10–16 (vs. 0–9)	0.89 (0.36 to 2.2)	0.79
Extracranial ISS>17 (vs. 0–9)	1.12 (0.35 to 3.58)	0.85
Marshall CT 3–4 (vs. 1–2)	9.06 (1.81 to 45.36)	0.007
Marshall CT 5–6 (vs. 1–2)	13.76 (2.12 to 89.2)	0.006
Psychiatric=yes (vs. no)	2.12 (1.02 to 4.4)	0.04
Cranial surgery/ICP monitor=yes (vs. no)	0.65 (0.11 to 3.87)	0.64
Hospital discharged alive		
Prior TBI=yes (vs. no)	0.83 (0.60 to 1.16)	0.29
Age (per year)	0.97 (0.96 to 0.98)	<0.001
Sex=female (vs. male)	0.76 (0.52 to 1.1)	0.14
GCS score 3–8 (vs. GCS score 9–12)	0.59 (0.44 to 0.79)	<0.001
Extracranial ISS=10–16 (vs. 0–9)	0.80 (0.51 to 1.24)	0.31
Extracranial ISS>17 (vs. 0–9)	0.41 (0.29 to 0.59)	<0.001
Marshall CT 3–4 (vs. 1–2)	0.71 (0.47 to 1.08)	0.11
Marshall CT 5–6 (vs. 1–2)	0.62 (0.45 to 0.85)	0.003
Psychiatric=yes (vs. no)	0.71 (0.5 to 1.01)	0.06
Cranial surgery/ICP monitor=yes (vs. no)	0.31 (0.22 to 0.43)	<0.001

Multivariable competing risk regression models were used to estimate the association of prior TBI with in-hospital mortality or hospital discharged alive over the length of hospital stay, censoring for patients with unfavorable discharge (nursing facility/nursing home, long-term acute care facility, hospice, or transfer to another hospital), and adjusted for age, sex, psychiatric history (yes vs. no), emergency department (ED) arrival GCS score (3–8 vs. 9–12), Marshall CT score (3–4, 5–6, vs. 1–2), extracranial ISS (10–16, ≥17 vs. 0–9), and cranial surgery/ICP monitor (yes vs. no).
GCS, Glasgow Coma Scale; ICP, intracranial pressure; ISS, Injury Severity Score; TBI, traumatic brain injury.

(6.8, 27.2) for no prior TBI, and rates of unfavorable discharge did not differ between prior TBI and no prior TBI (22% vs. 25%, respectively, p=0.76).

CIF curves showed a statistically significant higher probability of in-hospital mortality in subjects with prior TBI compared with without (p=0.013, figure 2), which was conserved in our sensitivity analysis (p=0.008, figure 3). In contrast, prior TBI did not confer statistically significant alterations to the likelihood of being discharged alive (p=0.34 in figure 2, p=0.55 in figure 3). Multivariable competing risk regression models showed a significant association between prior TBI and in-hospital mortality (aHR= 2.06, 95% CI 1.01 to 4.22) but not with hospital discharged alive (aHR=0.85, 95% CI 0.63 to 1.16) (table 2).

The increased subdistribution hazard for prior TBI and in-hospital mortality observed in our main analysis was conserved in our sensitivity analysis censoring unfavorable discharge (aHR=2.13 (1.04–4.37)) (table 3). Also, congruent with our main analysis, the likelihood of being discharged alive did not differ by prior TBI status in our sensitivity analysis (aHR=0.83 (0.60–1.16)) (table 3).

Statistically significant sociodemographic and clinical factors for higher risk of in-hospital mortality were older age and higher Marshall CT score, while factors significantly associated with higher likelihood of discharged alive were younger age, GCS score 9–12 (vs. GCS score 3–8), lower Marshall CT score (1–2 vs. 5–6), no cranial surgery/ICP monitor, and lower extracranial ISS (0–9 vs. >17) (table 2).

Outcomes at 3, 6, and 12 months

On multivariable logistic regression models, prior TBI did not demonstrate statistically significant associations with mortality or unfavorable functional outcomes at 3, 6, and 12 months (mortality: table 4; functional outcomes (GOSE): table 5), which corroborated our univariate analyses for these outcome measures (online supplemental table 2).

DISCUSSION

The relationship between prior TBI and acute hospital outcomes has not been well characterized in the contemporary msTBI population. Our retrospective analysis of prospectively enrolled patients with msTBI with ED arrival GCS score of 3–12 from 18 US level 1 trauma centers showed that prior TBI with alteration of consciousness or amnesia was associated with a higher risk of in-hospital mortality during acute care after controlling for

Table 4 Multivariable logistic regression models for mortality at 3, 6, and 12 months

	3-month model (n=307)		6-month model (n=294)		12-month model (n=269)	
Variables	Adjusted OR (95% CI)	Significance (P value)	Adjusted OR (95% CI)	Significance (P value)	Adjusted OR (95% CI)	Significance (P value)
Prior TBI=yes (vs. no)	1.96 (0.80 to 4.77)	0.14	1.75 (0.74 to 4.14)	0.21	1.59 (0.66 to 3.83)	0.30
Age (per year)	1.07 (1.04 to 1.09)	<0.0005	1.06 (1.04 to 1.09)	<0.0005	1.06 (1.04 to 1.08)	<0.0005
Sex=female (vs. male)	0.86 (0.33 to 2.23)	0.75	0.58 (0.22 to 1.51)	0.27	0.63 (0.24 to 1.61)	0.33
GCS score 3–8 (vs. GCS score 9–12)	2.17 (0.80 to 5.94)	0.13	2.11 (0.78 to 5.72)	0.14	2.45 (0.89 to 6.75)	0.08
Extracranial ISS=10–16 (vs. 0–9)	0.86 (0.27 to 2.71)	0.92	0.73 (0.23 to 2.27)	0.77	0.72 (0.23 to 2.27)	0.53
Extracranial ISS>17 (vs. 0–9)	1.16 (0.39 to 3.50)		1.23 (0.43 to 3.50)		1.59 (0.56 to 4.48)	
Marshall CT 3–4 (vs. 1–2)	6.64 (1.62 to 27.24)	0.001	5.27 (1.39 to 21.46)	0.003	5.35 (1.28 to 22.46)	0.001
Marshall CT 5–6 (vs. 1–2)	6.62 (2.41 to 18.17)		5.25 (2.00 to 13.80)		6.02 (2.30 to 15.76)	
Psychiatric=yes (vs. no)	1.66 (0.71 to 3.87)	0.24	2.29 (1.01 to 5.23)	0.049	2.26 (0.99 to 5.14)	0.05
Cranial surgery/ICP monitor=yes (vs. no)	2.24 (0.68 to 7.40)	0.19	3.01 (0.93 to 9.71)	0.07	2.84 (0.86 to 9.39)	0.09

Multivariable logistic regression models were performed to assess the associations between prior TBI history and mortality at 3, 6, and 12 months, adjusting for sociodemographic and clinical injury factors. The reference category of each factor is specified in parentheses. Statistical significance was assessed at p<0.05.
GCS, Glasgow Coma Scale; ICP, intracranial pressure; ISS, Injury Severity Score; TBI, traumatic brain injury.

sociodemographic, medical history, cranial injury and extracranial injury severity factors. These findings remained significant in our sensitivity analysis, confirming prior TBI as a predictor of in-hospital mortality as the first known report of this association in the acute msTBI cohort. Contrary to our hypothesis, prior TBI was not significantly associated with mortality or unfavorable functional outcomes up to 12 months after injury. Our findings are novel in underscoring the importance of ascertaining lifetime TBI history early during acute hospitalization for msTBI using a standardized and expeditious assessment tool.

Sociodemographic factors associated with prior TBI

In our cohort, male sex, psychiatric history, and history of substance abuse were reported at higher rates among patients with prior TBI compared with those without. Male sex[36] and psychiatric history[37 38] are known risk factors for TBI and are also associated with repetitive TBI.[7 39] Although no between-group differences were observed for alcohol or tobacco use, patients with prior TBI in our msTBI cohort reported more problems at work, school, and/or with relationships due to their substance use. As such, 'problematic' substance use as reported by the patient may comprise a novel risk factor for having multiple TBIs, as substance abuse is associated with risk-taking behaviors that facilitate reinjury.[40 41] It should be noted that the 'drug trouble' variable had a higher degree of missingness (~15%) in our cohort and its associations require validation in near-term studies. Nevertheless, our findings preliminarily support the clinical screening for problematic substance abuse and appropriate referrals for treatment to prevent cycles of further misuse and reinjury in TBI.

Prior TBI is a risk factor for in-hospital mortality

While reports have focused on prior TBI as a predictor of long-term outcomes after msTBI,[8 11] our study uniquely demonstrates that prior TBI with alteration of consciousness or amnesia may hasten in-hospital mortality. After adjusting for known sociodemographic, cranial injury, and extracranial injury-related predictors of post-TBI morbidity, our competing risk regression model showed prior TBI was associated with greater likelihood of in-hospital mortality but not hospital discharged alive over the duration of acute hospitalization. This constitutes the first report of the distinct subdistribution hazards associated with prior TBI between simultaneous acute clinical outcome events, extending prior literature in major acute injury and illness to acute TBI.[26–28]

Table 5 Multivariable logistic regression models for unfavorable outcomes at 3, 6, and 12 months

	3-month model (n=307)		6-month model (n=294)		12-month model (n=269)	
Variables	Adjusted OR (95% CI)	Significance (P value)	Adjusted OR (95% CI)	Significance (P value)	Adjusted OR (95% CI)	Significance (P value)
Prior TBI=yes (vs. no)	1.42 (0.72 to 2.82)	0.31	1.46 (0.72 to 2.99)	0.30	1.72 (0.77 to 3.84)	0.19
Age (per year)	1.04 (1.02 to 1.06)	<0.0005	1.04 (1.02 to 1.06)	<0.0005	1.05 (1.03 to 1.07)	<0.0005
Sex=female (vs. male)	1.83 (0.92 to 3.61)	0.08	1.53 (0.76 to 3.07)	0.24	1.50 (0.69 to 3.26)	0.31
GCS score 3–8 (vs. GCS score 9–12)	1.76 (0.91 to 3.38)	0.09	1.51 (0.74 to 3.06)	0.26	2.29 (1.02 to 5.15)	0.045
Extracranial ISS=10–16 (vs. 0–9)	2.17 (0.91 to 5.13)	0.017	1.88 (0.81 to 4.37)	0.07	1.66 (0.66 to 4.20)	0.13
Extracranial ISS>17 (vs. 0–9)	2.69 (1.25 to 5.78)		2.30 (1.05 to 5.04)		2.33 (0.96 to 5.66)	
Marshall CT 3–4 (vs. 1–2)	1.52 (0.53 to 4.31)	0.51	2.79 (0.97 to 8.02)	0.012	3.29 (0.96 to 11.21)	0.004
Marshall CT 5–6 (vs. 1–2)	1.42 (0.75 to 2.70)		2.64 (1.35 to 5.15)		3.36 (1.61 to 6.98)	
Psychiatric=yes (vs. no)	1.13 (0.60 to 2.12)	0.72	0.99 (0.51 to 1.91)	0.97	1.65 (0.80 to 3.41)	0.18
Cranial surgery/ICP monitor=yes (vs. no)	7.63 (3.64 to 16.02)	<0.0005	5.84 (2.58 to 13.19)	<0.0005	8.29 (3.00 to 22.90)	<0.0005

Multivariable logistic regression models were performed to assess associations between prior TBI history and unfavorable outcome (GOSE score=1–3 vs. 4–8) at 3, 6, and 12 months, adjusting for sociodemographic and clinical injury factors. The reference category of each factor is specified in parentheses. Statistical significance was assessed at p<0.05.
GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale-Extended; ICP, intracranial pressure; ISS, Injury Severity Score; TBI, traumatic brain injury.

Notably, our finding was conserved after censoring unfavorable discharge, implicating several potentially complex underlying bio-psycho-socio-ecological (BPSE) factors[1] specific to msTBI inpatients who die during hospitalization. In animal models, increased cerebral vulnerability to subsequent injuries has been associated with iterative TBIs,[42 43] and human studies have reported on the relationship between repetitive TBI and elevated circulating plasma antibody levels indicative of prior CNS injuries.[44] Such biologic phenomena and decreased cerebral reserve may partly explain the association between multiple TBIs and in-hospital mortality after acute msTBI, implicating lifetime TBI history as a potential marker of TBI-specific frailty. Additionally, patients with prior TBI may represent a distinct socioeconomic risk stratum due to their known associations with psychiatric history and substance use[8 45]; taken together, these factors may have additive effects on progression to in-hospital mortality after a subsequent msTBI and warrant further investigation.

Mortality or unfavorable outcomes within 12 months

Prior studies of repetitive TBI in msTBI have focused on chronic outcomes *beyond* 1 year.[8 11] In our cohort, statistically significant differences were not observed in mortality or unfavorable functional outcomes between patients with and without prior TBI at multiple timepoints *within* 12 months after injury after controlling for sociodemographic and injury-related factors. Taken together with our findings on in-hospital mortality, this suggests that in patients presenting with acute msTBI, prior TBI with alteration of consciousness or amnesia may selectively confer acute vulnerability to injury. Accordingly, factors with higher effect sizes such as age, injury severity, and cranial neurosurgical interventions showed more prominent associations with mortality and functional outcomes when combined in the same regression model with prior TBI history. It should be noted that, while not statistically significant, the aORs of prior TBI exceeded 1.0 across 3, 6, and 12-month mortality and unfavorable outcomes, thus the possibility of unmeasured factors in the context of sample size limitations is not excluded. While prior TBI was not associated with mortality or unfavorable outcomes within 12 months, certain longer term vulnerabilities may persist and should be examined in future studies.

Importance of collecting prior TBI history on acute hospitalization

Our findings show the importance of collecting prior TBI history in patients with msTBI early during hospitalization, given its association with in-hospital but not long-term mortality. Many clinicians have intuition about which patients may be susceptible to complications and mortality. Prior TBI history can be readily assessed using a validated, expeditious structured interview, recorded with other predictors of outcome (eg, psychiatric history, substance use, education, polytrauma), and integrated into the ED clinical workflow or a clinician's evaluation for patients with suspected cranial neurotrauma. As part of the BPSE model for TBI outcomes, lifetime TBI history objectively characterizes patients with msTBI and can inform clinicians regarding their triage and early risk stratification.

Limitations

We recognize several limitations in this work. The TRACK-TBI Study enrolled subjects at academic level 1 trauma centers in the USA, which limits the generalizability of our results for patients who are treated in other acute and non-represented settings. We did not investigate whether prior TBI is associated with withdrawal of life-sustaining therapy,[46] which occurs at variable rates after severe TBI[47] and remains an important area of future research when considering the additive consequences of repetitive TBIs. Although the OSU-TBI-ID is a validated and reliable self-report measure of lifetime TBI history, the data it records are inherently limited by recall bias. 'Drug trouble' emerged as a new variable associated with prior TBI; however, the extent of missingness, likely due to non-response bias during sociodemographic history collection, limited detailed examination of its associations with other variables or inclusion in multivariable models. Similarly, there were small amounts of missingness in certain baseline variables which limit interpretation. Despite this, we recognize that the identification of emerging variable 'drug trouble' constitutes the first step to clarifying their purported role in future TBI studies. Our analyses at 3, 6 and 12 months were partly limited by smaller sample sizes due to loss to follow-up. Dates of death were not available from the TRACK-TBI Study for subjects after they were discharged from their acute hospitalization, which limited granular assessments of postdischarge survival. We did not investigate the number of years elapsed between prior TBIs nor their recency due to variable self-response rates for these questions on the OSU-TBI-ID, which should be assessed in future studies. There were slight differences in the baseline characteristics of patients with complete prior TBI data compared with those without, and the relevance of these differences to our objectives is unclear. Baseline functional status and frailty were not assessed in our analysis and should be considered as part of a priori methodological planning in future topical studies. While the TRACK-TBI Study excluded patients deemed to have significant polytrauma that could interfere with the validity of outcome assessments at the time of enrollment, this was determined by the principal investigator at each site and therefore we further controlled for major extracranial injuries using the extracranial ISS. We acknowledge that procedural interventions for non-cranial body systems were not captured by our study, and how these interventions may be associated with msTBI outcomes in the context of prior TBI history warrants investigation. As prior TBI becomes better characterized as a risk factor for certain outcomes after acute TBI, its associated phenotypes may emerge to improve our understanding of TBI-specific frailty, prognostication, and likelihood of recovery.

CONCLUSIONS

In patients presenting with acute msTBI, prior TBI with alteration of consciousness or amnesia was independently associated with increased risk of in-hospital mortality, but not with mortality or unfavorable outcomes across the first 12 months after injury. This selective association underscores the importance of collecting standardized prior TBI history data early during hospitalization after acute msTBI to inform risk stratification. Prospective validation studies are needed to further elucidate the relationship between prior TBI history and early postinjury outcomes after msTBI.

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