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Outcome Prediction after Mild and Complicated Mild Traumatic Brain Injury: External Validation of Existing Models and Identification of New Predictors Using the TRACK-TBI Pilot Study

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Abstract

Although the majority of patients with mild traumatic brain injury (mTBI) recover completely, some still suffer from disabling ailments at 3 or 6 months. We validated existing prognostic models for mTBI and explored predictors of poor outcome after mTBI. We selected patients with mTBI from TRACK-TBI Pilot, an unselected observational cohort of TBI patients from three centers in the United States. We validated two prognostic models for the Glasgow Outcome Scale Extended (GOS-E) at 6 months after injury. One model was based on the CRASH study data and another from Nijmegen, The Netherlands. Possible predictors of 3- and 6-month GOS-E were analyzed with univariate and multi-variable proportional odds regression models. Of the 386 of 485 patients included in the study (median age, 44 years; interquartile range, 27–58), 75% ($n = 290$) presented with a Glasgow Coma Score (GCS) of 15. In this mTBI population, both previously developed models had a poor performance (area under the receiver operating characteristic curve, 0.49–0.56). In multivariable analyses, the strongest predictors of lower 3- and 6-month GOS-E were older age, pre-existing psychiatric conditions, and lower education. Injury caused by assault, extracranial injuries, and lower GCS were also predictive of lower GOS-E. Existing models for mTBI performed unsatisfactorily. Our study shows that, for mTBI, different predictors are relevant as for moderate and severe TBI. These include age, pre-existing psychiatric conditions, and lower education. Development of a valid prediction model for mTBI patients requires further research efforts.

Key words: GOS-E; prognostic models; TBI; validation

Introduction

Traumatic brain injury (TBI) is among the leading causes of death and disability. In the United States, at least 1.7 million patients a year seek some form of medical treatment.[1] TBI exacts significant health, social, and economic hardships on patients, their families, and health systems.[2,3] Approximately 70–90% of all TBIs are categorized as mild (mTBI), that is, presenting with a Glasgow Coma Scale (GCS) score of 13–15 after nonpenetrating head trauma. Although most mTBI patients will recover without residual impairments, persistent sequelae remain in a subgroup of 5–15%.[4] These complaints may include physical symptoms, behavioral disturbances,

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and cognitive dysfunction, any of which may interfere with return to work or resumption of social activities. Prognostic analyses are essential to identify patients at increased risk of developing residual sequelae and for leveraging resources to follow a more risk-prone subgroup. Closer observation and early intervention as part of clinical practice may alleviate the psychological burden of injury on these patients, as well as the related economic burden on society.

The heterogeneity in case definition of mTBI, the variety of outcome measures, and the variability in time elapsed for scoring both predictors and outcome render interpretation and comparison of results from mTBI prognostic studies difficult. Further, most studies only report on the association between predictors and outcome in univariate analyses.[5,6]

To our knowledge, only two studies have combined predictors and developed a prediction model specifically for mTBI.[7,8] One other model (Corticosteroid Randomization After Significant Head Injury; CRASH) was developed on patients with GCS 3–14 and thus captured a segment of the mTBI population, but not patients with GCS 15.[9,10] Further, none of the models have been externally validated in mTBI. Before a prognostic model can reliably be applied to clinical practice, external validation is required to determine generalizability. In this study, we aimed to evaluate the performance of existing mTBI prognostic models using a recent, prospective, unselected population of mTBI patients enrolled across three level 1 trauma centers in the United States and explore relevant predictors of poor outcome after mTBI.

Methods

Patient population

The study population consisted of patients included in the **T**ransforming **R**esearch **a**nd **C**linical **K**nowledge in TBI (TRACK-TBI) Pilot study.[11] In this study TBI patients age >16 years were enrolled upon arrival in the emergency departments (EDs) at San Francisco General Hospital (University of California San Francisco; UCSF), University of Pittsburgh Medical Center, and University Medical Center Brackenridge. All participants or their legally authorized representatives gave written informed consent. At follow-up outcome assessments, participants previously consented by legally authorized representative, if neurologically improved and capable, were consented for continuation in the study.

Inclusion criteria were presentation to study hospital within 24 h of injury and history of trauma to the head sufficient to triage to noncontrast head computed tomography (CT) using the American College of Emergency Physicians/Centers for Disease Control evidence-based joint practice guidelines.[12] We selected patients with mTBI and available 3- or 6-month outcome. All study protocols were approved by the institutional review boards at each participating level 1 trauma center.

Measures

Details on loss of consciousness, amnesia, and source of trauma were recorded upon admission and informed consent was obtained. GCS score was assessed by a neurosurgeon at admission.[13] Trained study personnel in the ED obtained demographic data, patient history, and clinical information from the patient. All patients underwent CT imaging at the time of initial presentation to the ED. Each patient's head CT was characterized using the National Institutes of Health/National Institute of Neurological Disorders and Stroke TBI Common Data Elements (TBI-CDEs).[14–16] Clinical brain CTs were transmitted to a radiology picture-archiving and communications system with software that allow controlled remote access for multiple users at study sites. To comply with the Health Insurance Portability and Accountability Act of 1996, the UCSF Quantitative Image Processing Center built a multiplatform tool that completely anonymized CT studies during the transmission process. Each CT was then reviewed by a single board-certified neuroradiologist blinded to demographic, socioeconomic, and clinical data, except gender and age, and scored on 26 of the 93 CDEs developed by the TBI-CDE neuroimaging working group.[17,18]

Outcome

The outcomes for this study were the Glasgow Outcome Scale Extended (GOS-E) at 3 and 6 months after injury.[19] The GOS-E provides eight categories of outcome: dead; vegetative state; lower severe disability; upper severe disability; lower moderate disability; upper moderate disability; lower good recovery; and upper good recovery. Ratings are based on patient consciousness, independence, ability to work, social and leisure activities, social relationships, and other sequelae of TBI. Upper good recovery (GOS-E score of 8) indicates return to preinjury baseline with no residual effects of the TBI.

Prediction models

Our literature search identified three prediction models that were developed (partly) on mTBI patients.[7–9] We could not validate the Stuhlemeijer and colleagues model because not all of the former's predictors were available in our data set.[7] We thus undertook to validate the Nijmegen and CRASH models.[9] The characteristics of the model are described in Table 1.

The Nijmegen model was built specifically for mTBI, with 6-month GOS-E <7 as the endpoint. Multivariable analysis of 1069 patients with GOS-E yielded age, Abbreviated Injury Score for head (AISh), Injury Severity Score (ISS) without head, and alcohol intoxication as significant predictors in the clinical model and number of hemorrhagic contusions and facial fractures as predictors of unfavorable outcome in the CT model and age, ISS without head, number of hemorrhagic contusions, and alcohol intoxication in the combined model.[8]

The Medical Research Council CRASH trial built and externally validated two prognostic models in mild, moderate, and severe TBI.[9] A basic model included age, GCS, pupillary reactivity, and presence of extracranial injury. In a CT model, additionally included were petechial hemorrhage, obliteration of third ventricle and cisterns, subarachnoid hemorrhage (SAH), mid-line shift, and nonevacuated hematoma emerged as predictors for mortality at 14 days and unfavorable outcome on the GOS (<4) at 6 months postinjury.[9] In this study, we only validated the models for 6-month unfavorable outcome. We note that the CRASH model excluded patients with GCS 15, a score that represents a majority of this subpopulation.

Statistical analysis

If patients had a missing outcome at 6 months, but an observed outcome at 3 months, the 3-month value was extrapolated to 6 months. Similarly, 6-month outcomes were interpolated when 3-month outcome was missing. Patients with missing outcome at both time points were excluded. Missing values in predictors were statistically imputed using single imputation with the AregImpute function in R statistical software (version 2.14; R Foundation for Statistical Computing, Vienna, Austria).

Patients' baseline characteristics were described by median and interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. These descriptive statistics were reported on the nonimputed data.

The prediction models were applied to the patients in the validation set, that is, a predicted probability of unfavorable outcome was calculated for each patient using the CRASH and Nijmegen models. Accordingly, the external validity of the models was assessed by studying calibration and discrimination. Calibration refers to the agreement between observed and predicted outcomes. The

Table 1. Characteristics of the Validated Models

Model	*Development population (*n*)*	*Predictors*	*Outcome*
Nijmegen	GCS 13–15 ($n=1069$)		6-month GOS-E < 7
Clinical model		-Age -AIS head -ISS without head -Alcohol intoxication	
CT model		-Number of hemorrhagic contusions -Facial fractures	
Combined model		-Age -ISS without head -Number of hemorrhagic contusions -Alcohol intoxication	
CRASH	GCS 3–14 ($n=10{,}008$)		6-month GOS < 4
Basic model		-Age -GCS -Pupillary reactivity -Extracranial injury	
CT model		Basic model plus -Petechial hemorrhage -Obliteration of third ventricle and cisterns -Subarachnoid hemorrhage -Mid-line shift -Nonevacuated hematoma	

CT, computed tomography; CRASH, Corticosteroid Randomization After Significant Head Injury; GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Score; ISS, Injury Severity Score; GOS-E, Glasgow Outcome Score Extended.

extent of over- or underestimation, relative to the observed and predicted rate, was explored graphically using validation plots.[20] We assessed calibration-in-the-large by fitting a logistic regression model with the logit of model predictions as an offset variable. The intercept indicates whether predictions are systematically too low or high and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and was estimated in a logistic regression model with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1. The area under the receiver operating characteristic curve (AUROC) was used to quantify the ability of the model to discriminate between patients who died versus survived. Because the development of the CRASH model did not include patients with GCS 15, we validated it both on patients with GCS 13–14 and on our total study population.

To further explore relevant predictors of 3- and 6-month GOS-E, we selected 21 possible predictors from the literature and based on clinical knowledge. These were analyzed in univariate and multivariable proportional odds regression models with 3- and 6-month GOS-E as ordinal outcomes. This means that the full range of the GOS-E is considered instead of dichotomizing at a fixed point (e.g., favorable vs. unfavorable outcome). Simulation studies have shown that ordinal analysis is more efficient than dichotomization, also when the proportional odds assumption is violated. Each predictor was tested in the univariate models, and those with a p value of 0.30 in both the 3- and 6-month model were selected for inclusion in the multi-variable models. The liberal p value was motivated by the fact that we performed an exploratory analysis in a relatively small sample size and did not want to exclude possible predictors.

All analyses were performed with R statistical software (version 2.14; R Foundation for Statistical Computing).

Results

Patient population

TRACK-TBI Pilot enrolled 485 patients with mTBI, including 480 with nonpenetrating injury who were eligible for our study. Patients with penetrating brain injury ($n=5$) or missing outcome at both 3 and 6 months after injury ($n=94$) were excluded. A total of 386 patients were included in our analysis. The median age of our population was 44 years (IQR, 27–58). The majority ($n=271$; 70%) was male. Most patients ($n=290$; 75%) presented with a GCS of 15 and two reactive pupils. Most patients were injured in a motor vehicle traffic accident ($n=179$; 47%). Almost one third ($n=118$; 31%) of the patients had self-reported psychiatric (mental health) history, which was obtained at the time of injury through patient interview using a checklist of common psychiatric conditions as defined by the TBI CDE V1.0 (e.g., anxiety, depression, sleep disorders, post-traumatic stress, bipolar disorder, schizophrenia, and others). Patients need not have been formally diagnosed with a mental health disturbance; however, to qualify as ''positive'' for psychiatric history, the patient must deem the condition to be significantly disturbing for their baseline quality of life. More then half ($n=198$; 53%) of the patients reported history of previous TBI as defined by external force injury to the head. Over half of the patients ($n=232$; 60%) had no visible CT pathology (Marshall's CT classification I).[21] The most common pathologies observed on CT were contusions (61; 16%), SAH (103; 27%), and facial fractures (53; 14%). Most baseline variables had very few missing values (< 2%), but the AISh, ISS, and extracranial injury had almost 40% missing values. Alcohol intoxication, as measured by blood alcohol levels, was missing in almost 60% of cases (Table 2).

At 3 months after injury, 116 (24%) were lost to follow-up. Of those with observed outcomes, 33% ($n=121$) completely recovered (GOS-E, 8) and 32% ($n=118$) had some remaining symptoms (GOS-E, 7). Of the remaining one third of the sample 2% ($n=6$) died, 4% ($n=15$) were severely disabled (GOS-E, 3–4), and 28% ($n=104$) were moderately disabled (GOS-E, 5–6; Table 3).

After 6 months, an additional 181 (38%) patients were lost to follow-up. Of those with observed outcome, 34% ($n=102$) made a complete recovery (GOS-E, 8) at 6 months and 30% ($n=89$) had

Table 2. Patient Characteristics ($N = 386$[a])

Characteristic	*Missing*	No. (%)
Age (median, IQR)	0	44 (27–58)
Male gender	0	271 (70)
Cause	4	
Road traffic accident		179 (47)
Fall		133 (35)
Assault		54 (14)
Struck by/struck against person or object		14 (6)
Other		2 (1)
GCS	0	
15		290 (75)
14		81 (21)
13		15 (4)
Pupil reactivity	61	
Both reactive		319 (98)
One reactive		5 (2)
None reactive		1 (0)
Psychiatric medical history	0	118 (31)
Hypoxia	2	23 (6)
Hypotension	1	13 (3)
Previous TBI (with and without hospital admission)	11	198 (53)
Education	12	
Low		37 (10)
Middle		202 (54)
High		135 (36)
Alcohol intoxication	228	52 (33)
ISS (median, IQR)	152	16 (10–18)
AIS head	152	
0		34 (15)
1		6 (3)
2		27 (12)
3		70 (30)
4		83 (35)
5		14 (6)
Extracranial injury	152	53 (23)
Marshall CT	0	
1		232 (60)
2		134 (35)
3		9 (2)
4		4 (1)
5		5 (1)
6		2 (1)
Facial fracture	0	53 (14)
EDH	0	12 (3)
tSAH	1	103 (27)
Mid-line shift	1	10 (3)
Third ventricle obliteration	2	11 (3)
Contusions	1	61 (16)
Petechial hemorrhage	1	3 (1)

[a]Of 485 patients, 5 were excluded because they had penetrating injury and 94 had missing outcome, leaving 386 for inclusion.

IQR, interquartile range; GCS, Glasgow Coma Scale; TBI, traumatic brain injury; ISS, Injury Severity Score; AIS, Abbreviated Injury Score; CT, computed tomography; EDH, extradural haematoma; tSAH, traumatic subarachnoid hemorrhage.

some remaining symptoms (GOS-E, 7). Three percent ($n = 9$) had died, 3% ($n = 9$) were severely disabled (GOS-E, 3–4), and 30% ($n = 90$) were moderately disabled (GOS-E, 5–6).

Between 3 and 6 months after injury, 3 patients died and another 65 deteriorated, based on worsening GOS-E. Conversely, 66 patients showed improved GOS-E scores between 3 and 6 months. The 94 patients with missing outcome at both time points were excluded from this analysis.

Model validation

The Nijmegen models performed poorly in the external validation, with AUROCs of 0.52 (95% confidence interval [CI], 0.49–0.56; clinical model), 0.55 (95% CI, 0.49–0.55; CT model), and 0.56 (95% CI, 0.49–0.56; combined model) (Fig. 1). The CRASH models performed poorly in the total mTBI population, including GCS 15 (AUROC basic model, 0.49; 95% CI, 0.43–0.70; AUROC CT model, 0.49; 95% CI, 0.42–0.66) (Fig. 2). However, performance was very well with AUROCs of 0.90 (95% CI, 0.82–0.97; basic model) and 0.91 (95% CI, 0.85–0.98; CT model) (Fig. 3) in the population they were developed on. The proportion of unfavorable outcome in TRACK-TBI Pilot was overestimated by most models. For example, the predicted proportion of patients with unfavorable outcome by the CRASH CT model was 12%; however, the actual observation of unfavorable outcome at 6 months was 8%.

Predictors

In univariate analyses (Table 4), we identified a large number of characteristics as potential predictors of outcome both 3- and 6-month GOS-E: age; cause of injury; GCS; pupil reactivity; psychiatric medical history; hypoxia; hypotension; education; ISS; extracranial injury; SAH; mid-line shift; and third ventricle obliteration and contusions (all $p < 0.30$ for both 3- and 6-month GOS-E; Table 4). Some predictors had a different effect on 3-versus 6-month outcome. A GCS of 13 or 14 was a strong predictor for a lower 6-month GOS-E (odds ratio [OR] = 0.3; $p = 0.015$), but less predictive for lower 3-month GOS-E (OR = 0.5–0.6; $p = 0.299$). In contrast, the CT characteristics were more predictive of 3-month outcome, compared with 6-month outcome (e.g., SAH: 3-month OR = 2.2, $p < 0.001$; 6-month OR = 1.3, $p = 0.224$).

In multivariable analyses (Table 5), the strongest predictors of both lower 3- and 6-month GOS-E were older age (OR, 1.2; $p < 0.001$), history of psychiatric conditions (OR = 2.2–2.4; $p < 0.001$), and lower education (OR, 0.4–0.8; $p < 0.05$; Table 4). Injury caused by assault and extracranial injury were important predictors of poorer outcome at both time points ($p = 0.05$–0.1). Finally, a lower GCS was predictive of lower 6-month GOS-E (OR, 0.3–0.4; $p = 0.039$).

Discussion

In this study, we externally validated two prognostic models for prediction of outcome after mTBI. We found that both models performed unsatisfactorily in our validation data set. In exploratory analyses, we identified older age, pre-existing psychiatric conditions, lower education, injury caused by assault and extracranial injury, and lower GCS as predictors of 3- and 6-month GOS-E.

Study population

We included only patients with a so-called mTBI, as defined by a GCS 13–15. However, the population did contain some patients

Table 3. Outcome[a]

3-month GOS-E / *6-month GOS-E*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*Unknown*	*Total (%)*
1	6	0	1	0	1	0	1	0	0	9 (3[b])
2	0	0	0	0	0	0	0	0	0	0 (0[b])
3	0	0	2	1	1	0	0	0	1	5 (2[b])
4	0	0	2	1	0	0	1	0	0	4 (1[b])
5	0	0	1	0	14	10	6	4	3	38 (13[b])
6	0	0	0	3	9	13	21	3	3	52 (17[b])
7	0	0	0	1	5	14	43	18	8	89 (30[b])
8	0	0	0	0	2	7	22	64	7	102 (34[b])
Unknown	0	0	0	3	9	19	24	32	94	181 (38[c])
Total (%)	6 (2[b])	0 (0[b])	6 (2[b])	9 (2[b])	41 (11[b])	63 (17[b])	118 (32[b])	121 (33[b])	116 (24[c])	480

[a]$n = 480$.
[b]Percentage of patients with observed outcome.
[c]Percentage of all patients.
GOS-E, Glasgow Outcome Score Extended.

Table 4. Univariate Predictors of 3- and 6-Month GOS-E[a]

Predictors	*Common OR (95% CI) (3 months)*	p *value*	*Common OR (95% CI) (6 months)*	p *value*
Age (per 10 years)	1.2 (1.1–1.3)	< 0.001	1.2 (1.1–1.3)	0.002
Male gender	0.9 (0.6–1.4)	0.678	0.8 (0.6–1.2)	0.316
Cause		0.021		< 0.001
MV	Ref		Ref	
Fall	1.4 (0.9–2.1)		1.6 (1.1–2.4)	
Assault	2.2 (1.3–3.6)		2.6 (1.5–4.5)	
Struck by/strike against	1.3 (0.5–3.4)		0.6 (0.2–1.7)	
GCS		0.299		0.015
13	Ref		Ref	
14	0.6 (0.3–1.6)		0.3 (0.1–1.0)	
15	0.5 (0.2–1.3)		0.3 (0.3–0.7)	
No or one pupil reactive	2.4 (0.6–9.6)	0.205	3.8 (1.1–13.5)	0.039
Psychiatric medical history	2.2 (1.5–3.3)	< 0.001	2.9 (1.9–4.2)	< 0.001
Hypoxia	2.8 (1.3–5.9)	0.009	2.7 (1.2–6.1)	0.018
Hypotension	1.8 (0.7–4.8)	0.206	2.2 (0.8–5.8)	0.112
Education		0.050		0.012
Low	Ref		Ref	
Middle	1.0 (0.5–1.9)		0.7 (0.4–1.4)	
High	0.6 (0.3–1.1)		0.4 (0.2–0.8)	
Alcohol intoxication	0.9 (0.6–1.3)	0.565	1.2 (0.8–1.7)	0.463
ISS	1.03 (1.01–1.06)	0.026	1.02 (0.99–1.04)	0.156
AIS head	1.2 (1.0–1.3)	0.017	1.03 (0.90–1.12)	0.701
Extracranial injury	1.7 (1.1–2.7)	0.012	1.6 (1.0–2.4)	0.044
Marshall's CT		0.002		0.836
1	Ref		Ref	
2	1.9 (1.3–2.8)		1.0 (0.8–1.5)	
3–4	2.9 (1.2–7.6)		1.7 (0.7–4.1)	
5–6	15.5 (3.2–76.2)		8.5 (1.8–40.8)	
Facial fracture	1.4 (0.9–2.4)	0.147	1.3 (0.8–2.3)	0.307
EDH	1.0 (0.4–2.6)	0.986	0.3 (0.1–0.9)	0.033
tSAH	2.2 (1.5–3.3)	< 0.001	1.3 (0.9–1.9)	0.224
Midline shift	7.8 (2.2–27.6)	0.013	3.2 (0.9–11.6)	0.070
Third ventricle obliteration	8.2 (2.6–26.4)	< 0.001	3.2 (1.0–10.3)	0.050
Contusions	1.9 (1.2–3.1)	0.008	1.4 (0.9–2.3)	0.171
Petechial hemorrhage	2.0 (0.3–12.7)	0.473	0.5 (0.1–3.5)	0.527

[a]$n = 386$.
GOS-E, Glasgow Outcome Score Extended; MV, motor vehicle; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; AIS, Abbreviated Injury Score; CT, computed tomography; EDH, extradural haematoma; tSAH, traumatic subarachnoid hemorrhage; OR, odds ratio, CI, confidence interval; Ref, reference.

Table 5. Multivariable Predictors of 3- and 6-Month Ordinal GOS-E

Predictor	*Common OR (95% CI) (3 months)*	p *value*	*Common OR (95% CI) (6 months)*	p *value*
Age (per 10 years)	1.2 (1.1–1.4)	< 0.001	1.2 (1.1–1.4)	< 0.001
Cause		0.103		0.039
MV	Ref		Ref	
Fall	0.9 (0.6–1.4)		1.0 (0.6–1.6)	
Assault	1.9 (1.1–3.4)		2.0 (1.1–3.6)	
Struck by/strike against	1.1 (0.4–3.4)		0.5 (0.2–1.4)	
GCS		0.481		0.061
13	Ref		Ref	
14	0.8 (0.3–2.3)		0.4 (0.1–1.2)	
15	0.6 (0.2–1.7)		0.3 (0.1–0.9)	
No or one pupil reactive	1.0 (0.2–4.4)	0.974	2.1 (0.6–7.5)	0.253
Psychiatric medical history	2.2 (1.4–3.2)	< 0.001	2.4 (1.6–3.7)	< 0.001
Hypoxia	2.0 (0.9–4.4)	0.101	1.8 (0.7–4.2)	0.193
Hypotension	1.4 (0.5–3.6)	0.507	1.6 (0.6–4.1)	0.369
Education		0.032		0.016
Low	Ref		Ref	
Middle	0.8 (0.4–1.6)		0.7 (0.4–1.4)	
High	0.5 (0.2–1.0)		0.4 (0.2–0.9)	
ISS per point	1.02 (0.99–1.04)	0.250	1.00 (0.98–1.03)	0.759
Extracranial injury	1.7 (1.0–2.7)	0.045	1.5 (0.9–2.4)	0.105
tSAH	1.6 (0.9–2.9)	0.095	0.9 (0.5–1.5)	0.579
Mid-line shift	1.6 (0.3–8.6)	0.594	0.8 (0.1–5.2)	0.844
Contusion	1.3 (0.7–2.6)	0.404	1.6 (0.8–3.1)	0.176
Third ventricle obliteration	4.1 (0.8–20.6)	0.084	3.4 (0.6–20.2)	0.181

AUROC 3-month model = 0.68; AUROC 6-month model = 0.69.

GOS-E, Glasgow Outcome Score Extended; MV, motor vehicle; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; tSAH, traumatic subarachnoid hemorrhage; OR, odds ratio, CI, confidence interval; Ref, reference.

with one or two unreactive pupils, an AISh of 4 or 5, or a Marshall's CT classification of 5 or 6, characteristics that indicate a more severe head injury. This illustrates the limitations of a unidimensional approach to classification of TBI. More than half of the patients reported a previous head injury. This might be an overestimation given that it was self-reported.

Outcome

Our findings that one third of the patients made a complete recovery (GOS-E, 8), one third had some minor remaining symptoms (GOS-E, 7), and the final one third had significant disabling complaints at 3 and even 6 months are consistent with previous research.[7] Although our study population might include somewhat more severe patients than the general population as a result of the case mix at our level 1 trauma enrollment centers, these results illustrate that the consequences of mTBI should not be underestimated. The overall outcome distribution was similar at 3 and 6 months, but there were some patients who died between 3 and 6 months and some that deteriorated. Unfortunately, we were unable to trace whether those that deteriorated did so as a result of the initial head injury or from other events. The lost to follow-up percentage increased to 38% at 6 months. This lost to follow-up percentage is similar to, or better than, other TBI studies.[22–24] However, higher follow-up rates are generally achieved in randomized, controlled trials. TBI patients are a difficult group to follow, and researchers should recognize the fact that it requires substantial resources to achieve acceptable follow-up rates in TBI studies.

Approximately half of the patients (94 of 181) who were lost to follow-up at 6 months also did not have a 3-month outcome. Of the patients with observed outcome at 3 months, the majority (56 of 87) had a GOS-E of 7 or 8. This is consistent with previous findings that willingness to participate in research is less in those who fully recover and may result in an overestimation of the rate of unfavorable outcome.[25] Given that it is unlikely that predictors have differential relative effects in patients with more-favorable outcome, we do not expect the results of the prognostic analyses to be affected by the missing outcomes.

Models

With AUROCs of 0.52–0.56, the Nijmegen model's ability to discriminate between patients with favorable and unfavorable outcome was hardly better than chance (AUROC = 0.5). The reason for this poor performance is likely to be related to the original modeling strategy used in this study. Their development sample included 1069 patients, of which 257 had unfavorable outcome. In this sample, 33 possible predictors were tested, corresponding to one predictor for seven outcome events. A rule of thumb in prognostic modeling is that at least 10–20 outcome events are required to test one predictor. Testing too many predictors for the sample size may result in models that are overfitted, resulting in a good apparent performance in the development data, but poor performance at external validation. The amount of overfitting can be assessed and quantified with internal validation (e.g., in a bootstrap procedure), but this was not done by Jacobs and colleagues. The

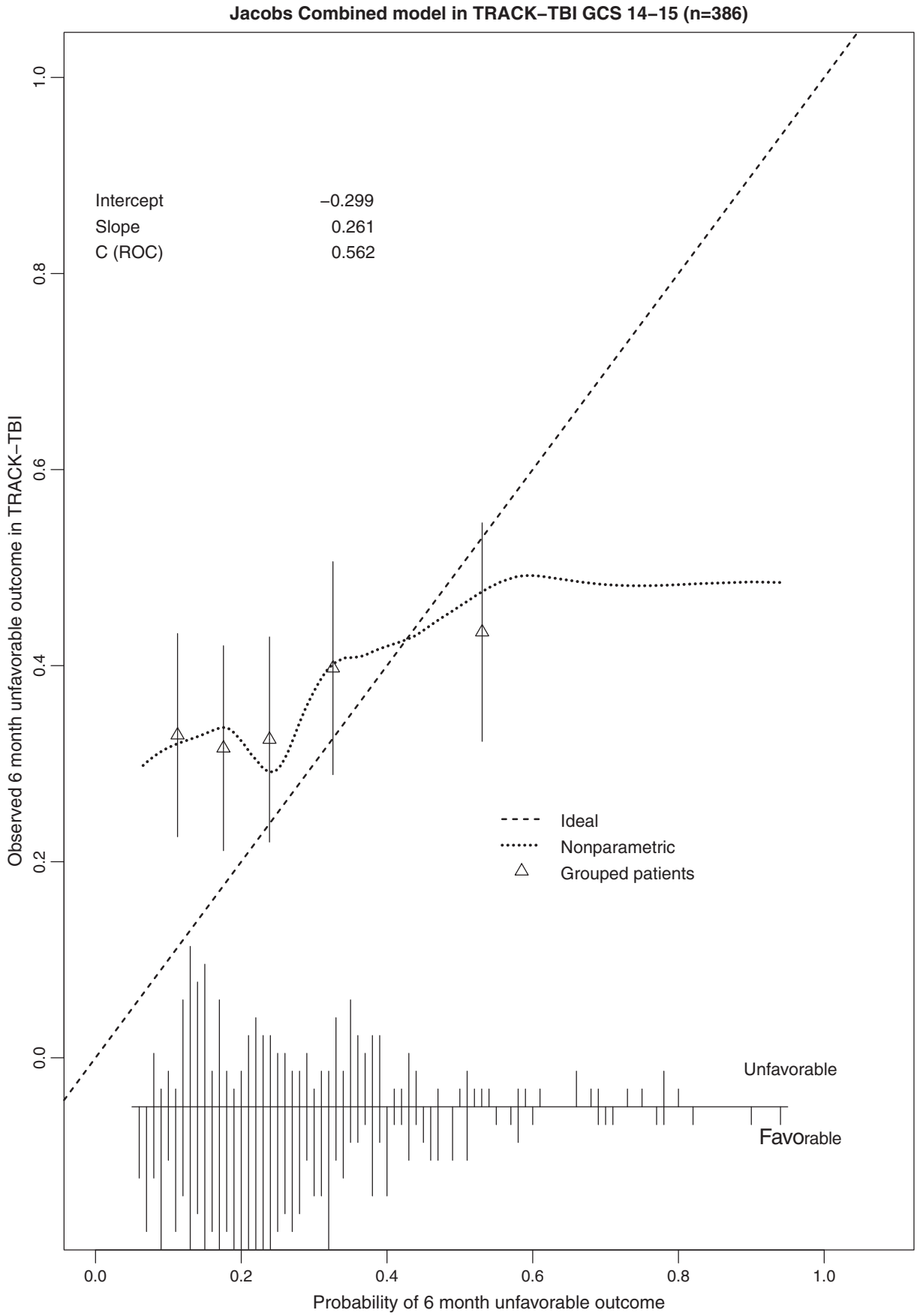

FIG. 1. Calibration plot Jacobs combined model. x-axis shows predicted probabilities by the model in quintiles of patients (triangles with horizontal lines as 95% confidence intervals); y-axis shows observed probabilities. Dotted diagonal represents perfect predictions. Spikes along the x-axis are numbers of patients with favorable and unfavorable observed outcomes. ROC, receiver operating characteristic.

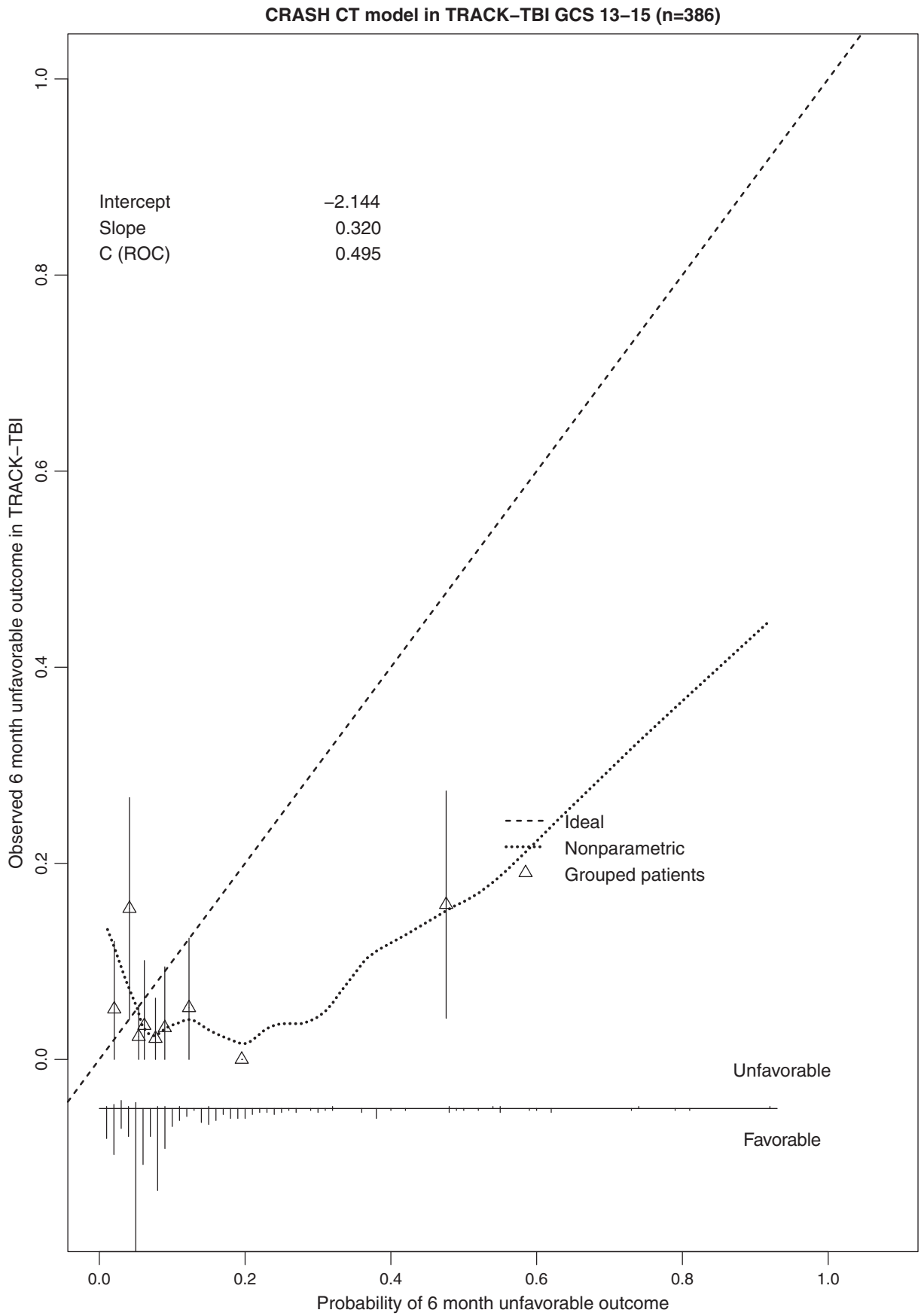

FIG. 2. Calibration plot CRASH computed tomography model. x-axis shows predicted probabilities by the model in quintiles of patients (triangles with horizontal lines as 95% confidence intervals); y-axis shows observed probabilities. Dotted diagonal represents perfect predictions. Spikes along the x-axis are numbers of patients with favorable and unfavorable observed outcomes. ROC, receiver operating characteristic.

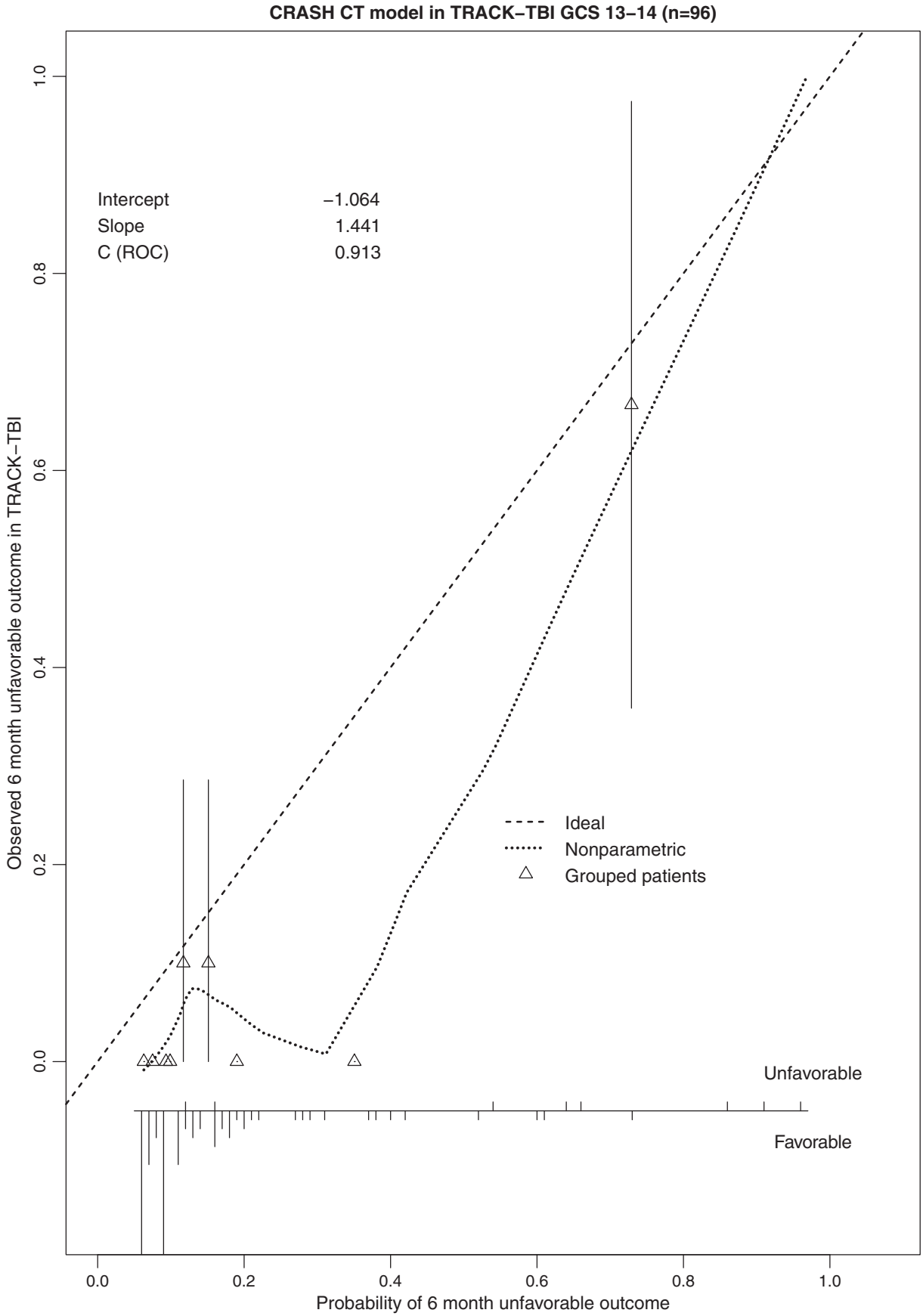

FIG. 3. Calibration plot CRASH computed tomography model (original population). x-axis shows predicted probabilities by the model in quintiles of patients (triangles with horizontal lines as 95% confidence intervals); y-axis shows observed probabilities. Dotted diagonal represents perfect predictions. Spikes along the x-axis are numbers of patients with favorable and unfavorable observed outcomes. ROC, receiver operating characteristic.

difference between the discriminative ability in the development data (AUROCs, 0.57–0.71) and in the validation data likely indicate that the Jacobs model is overfitted, but may also be attributed to true differences in prognostic relations.

The CRASH models discriminated equally poor in the total mTBI population, with AUROCs of 0.49–0.50. However, the CRASH models were not developed for patients with a GCS of 15, which was the majority of our sample. When patients with GCS 15 were excluded, the CRASH models discriminated well. In contrast to the Nijmegen models, the CRASH models were developed by testing 14 predictors in 3556 outcome events and were internally and externally validated in moderate and severe TBI.[26] It should be noted that the outcome predicted by the CRASH models was GOS < 4, whereas the Nijmegen model predicts GOS-E < 7. Possibly, it is easier to discriminate between patients above or below a cutoff in the middle of the GOS-E, compared with a cutoff at the higher end. This is supported by the finding that our ordinal multivariable models had AUROCs of 0.68–0.69, representing the discriminative ability over the complete GOS-E. When the models were refitted with CRASH outcome GOS < 4, the AUCs increased to 0.86. In all, the validation of these previously developed models supports the need for further research to develop valid prognostic models for mTBI patients.

Predictors of unfavorable outcome

Age, pre-existing psychiatric conditions, and lower education were the strongest predictors for both 3- and 6-month GOS-E in our data. Older age is a recognized predictor of poorer outcome in many diseases, including TBI, and our finding is consistent with the literature.[27] Pre-existing psychiatric conditions are less often studied, but also have been found to predict unfavorable outcome.[28] While speculative, it is possible that individuals with a pre-existing mental health condition may have less reserve to overcome the additional strain of an mTBI. Alternatively, symptoms that relate primarily to this comorbidity may falsely be attributed to the head injury.[29] More highly educated patients may have more-adaptive coping skills that allow them to return to their previous levels of functioning.[7]

Additional strong predictors of lower 6-month GOS-E were injury caused by assault, extracranial injury, and lower GCS. GCS is an indication of more-severe injury resulting in less favorable outcome. Violence as a cause of injury has been previously described as a predictor of fatigue after mTBI. The researchers suggested that post-traumatic stress might play a role in this relation.[28] Extracranial injury may result in disability independent of the head injury and has been described as a predictor of poor outcome before, especially in unselected TBI populations.[30]

It has been suggested that in moderate and severe TBI, outcome is determined by what ''the injury brings to the patient'' whereas in mTBI it is what ''the patient brings to the injury,'' and our data support this statement. Generally accepted prognostic models for moderate and severe TBI include, in addition to age, indicators of injury severity, such as GCS, pupillary reactivity, and CT parameters.[9,10,26] These predictors are less relevant in mTBI. Here, indicators of social background, history of psychiatric conditions, assault as cause of injury, and low education seem to be predictive of poorer outcome. However, the combination of pre-existing psychiatric conditions, low education, and assault as a cause of injury as predictors of 6-month outcome poses the question of whether persistent complaints are fully attributable to the TBI. Future studies that follow up with more-sensitive and -specific outcome measures in larger cohorts are required to answer this question. In this study, we neither aimed nor had enough patients to fully disentangle the mechanisms causing poor outcome. This would be essential to target treatment to patients at high risk for poor outcome and should be a main focus of future studies and large ongoing efforts such as CENTER-TBI and TRACK-TBI.

The predictors we combined in our multi-variable analysis had a moderate discriminative ability (AUROCs, 0.68''0.69). Emerging technologies that could improve prognostication in mTBI include proteomic biomarkers,[31–33] genetic factors,[34–36] and improved imaging biomarkers, including magnetic resonance imaging.[37] Additionally, prediction models for mTBI may require more-sensitive and -specific outcome measures beyond the GOS-E.

We recognize several limitations to our study. We included patients with GCS 13–15, which are classified in the category of mTBI. However, there were patients with one or two unreactive pupils, an AISh of 4 or 5, or a Marshall's CT classification of 5 or 6 (indicative of ''complicated'' mTBI with pathological head CT findings), all indicating quite severe injury. More than half of the patients reported previous head injury, which may be an overestimation given that it was self-reported without necessarily requiring hospital admission. Pre-existing psychiatric conditions proved to be one of the strongest predictors to poorer outcome. A goal of the TRACK-TBI Pilot Study was to evaluate the feasibility of implementing the TBI CDEs V1.0, which did not include a validated structured interview for preinjury psychiatric history. Even though we implemented the highest level of granularity for baseline data collection, we were unable to capture the specific types, durations, and formal diagnoses of pre-existing psychiatric conditions. In moving forward, establishing a standard set of tools and questionnaires to obtain this level of granularity will be helpful in evaluating the true associations among pre-existing mental health conditions and post-TBI outcome.

Conclusion

Reliable outcome prediction in mTBI is important for clinical practice. Identifying patients at increased risk of unfavorable outcome permits targeting closer observation and early intervention, which may reduce the psychological burden of injury on patients, as well as the related economic burden on society. Our study demonstrates that existing models for mTBI perform unsatisfactorily. We tested 21 variables in ordinal analysis of 386 patients, which is 1 in 18 and thus reasonable from a statistical perspective. Although we have found some strong predictors of poor outcome, such as age and history of psychiatric condition, given the sample size, we consider the results of our prognostic analysis as hypothesis generating. These predictors will need further validation in ongoing prospective, longitudinal studies, such as those that are part of the International TBI Research Initiative.[38,39]

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Author Disclosure Statement

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