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CLINICAL ARTICLE

Performance of the IMPACT and CRASH prognostic models for traumatic brain injury in a contemporary multicenter cohort: a TRACK-TBI study

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OBJECTIVE The International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) and Corticosteroid Randomization After Significant Head Injury (CRASH) prognostic models for mortality and outcome after traumatic brain injury (TBI) were developed using data from 1984 to 2004. This study examined IMPACT and CRASH model performances in a contemporary cohort of US patients.

METHODS The prospective 18-center Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study (enrollment years 2014–2018) enrolled subjects aged ≥ 17 years who presented to level I trauma centers and received head CT within 24 hours of TBI. Data were extracted from the subjects who met the model criteria (for IMPACT, Glasgow Coma Scale [GCS] score 3–12 with 6-month Glasgow Outcome Scale–Extended [GOSE] data [n = 441]; for CRASH, GCS score 3–14 with 2-week mortality data and 6-month GOSE data [n = 831]). Analyses were conducted in the overall cohort and stratified on the basis of TBI severity (severe/moderate/mild TBI defined as GCS score 3–8/9–12/13–

ABBREVIATIONS BPSE = bio-psycho-socio-ecological; CDE = Common Data Element; CENTER-TBI = Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; CRASH = Corticosteroid Randomization After Significant Head Injury; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale–Extended; IMPACT = International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury; Lab = Laboratory; NINDS = National Institute of Neurological Disorders and Stroke; TBI = traumatic brain injury; TRACK-TBI = Transforming Research and Clinical Knowledge in Traumatic Brain Injury; tSAH = traumatic subarachnoid hemorrhage.

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14), age (17–64 years or ≥ 65 years), and the 5 top enrolling sites. Unfavorable outcome was defined as GOSE score 1–4. Original IMPACT and CRASH model coefficients were applied, and model performances were assessed by calibration (intercept [< 0 indicated overprediction; > 0 indicated underprediction] and slope) and discrimination (c-statistic).

RESULTS Overall, the IMPACT models overpredicted mortality (intercept −0.79 [95% CI −1.05 to −0.53], slope 1.37 [1.05–1.69]) and acceptably predicted unfavorable outcome (intercept 0.07 [−0.14 to 0.29], slope 1.19 [0.96–1.42]), with good discrimination (c-statistics 0.84 and 0.83, respectively). The CRASH models overpredicted mortality (intercept −1.06 [−1.36 to −0.75], slope 0.96 [0.79–1.14]) and unfavorable outcome (intercept −0.60 [−0.78 to −0.41], slope 1.20 [1.03–1.37]), with good discrimination (c-statistics 0.92 and 0.88, respectively). IMPACT overpredicted mortality and acceptably predicted unfavorable outcome in the severe and moderate TBI subgroups, with good discrimination (c-statistic ≥ 0.81). CRASH overpredicted mortality in the severe and moderate TBI subgroups and acceptably predicted mortality in the mild TBI subgroup, with good discrimination (c-statistic ≥ 0.86); unfavorable outcome was overpredicted in the severe and mild TBI subgroups with adequate discrimination (c-statistic ≥ 0.78), whereas calibration was nonlinear in the moderate TBI subgroup. In subjects ≥ 65 years of age, the models performed variably (IMPACT-mortality, intercept 0.28, slope 0.68, and c-statistic 0.68; CRASH–unfavorable outcome, intercept −0.97, slope 1.32, and c-statistic 0.88; nonlinear calibration for IMPACT–unfavorable outcome and CRASH-mortality). Model performance differences were observed across the top enrolling sites for mortality and unfavorable outcome.

CONCLUSIONS The IMPACT and CRASH models adequately discriminated mortality and unfavorable outcome. Observed overestimations of mortality and unfavorable outcome underscore the need to update prognostic models to incorporate contemporary changes in TBI management and case-mix. Investigations to elucidate the relationships between increased survival, outcome, treatment intensity, and site-specific practices will be relevant to improve models in specific TBI subpopulations (e.g., older adults), which may benefit from the inclusion of blood-based biomarkers, neuroimaging features, and treatment data.

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KEYWORDS clinical prediction rules; Glasgow Outcome Scale; mortality; prognosis; statistical models; traumatic brain injury

Traumatic brain injury (TBI) results from heterogeneous pathophysiological mechanisms that are influenced by varying baseline and injury-related risk factors, leading to variable outcomes and challenges in prognostication.[1] Inadequate prognostication has hindered cohort selection and risk stratification in TBI clinical trials, as well as patient/caregiver counseling and informed care planning. The International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) and the Medical Research Council Corticosteroid Randomization after Significant Head Injury (CRASH) prognostication models have undergone considerable external validation.[2–6] The IMPACT and CRASH models were developed using prospectively collected multicenter cohort data between 1984 and 1997 (n = 8509) and 1999 and 2004 (n = 10,008) in TBI patients with initial Glasgow Coma Scale (GCS) scores 3–12 and 3–14, respectively. Both models analyzed clinical, radiological, and laboratory factors to determine the strongest predictors of 2-week (CRASH) and 6-month (IMPACT) mortality, as well as 6-month unfavorable outcome (both models), to construct representative prognostic models.

Although IMPACT and CRASH models have shown adequate performance across external validation studies,[6–8] it should be noted that these models are based on data acquired 2–4 decades ago and primarily in hospital systems outside of North America. This may limit their generalizability with respect to geographical location, updated evidence, and advancements in TBI care. Additionally, a majority of validation studies were conducted using single-institution data.[7–9] Assessment of model performance using updated multi-institutional data is needed.

Importantly, the extent to which a statistical prediction model accurately estimates outcome and/or risk can be characterized by two properties: calibration and discrimination.[10] Calibration assesses the accuracy of predicted versus observed outcomes across the modeled dataset and is evaluated through a calibration plot, with the intercept indicating the extent of model overprediction or underprediction. Discrimination assesses how well the model differentiates patients at high versus low risk for having an event and can be measured using area under the receiver operating characteristic curve or c-statistic. A model can have excellent discrimination and poor calibration, i.e., it separates risk well, but has inaccurate model–predicted outcome probabilities. Prior IMPACT and CRASH validation studies have reported model performances based primarily on discrimination.[10–12] Furthermore, model performance may be adequate when examining an overall patient cohort but may not accurately estimate risk in subgroups. Therefore, evaluation of model performance using both metrics and in different risk strata of TBI patients remains critical to assessment of clinical utility.

The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study enrolled acute TBI patients from 18 US level I trauma centers between 2014 and 2018.[13] Similar to the IMPACT and CRASH trials, TRACK-TBI collected data on clinical, laboratory, radiological, mortality, and outcome characteristics, with the additional strength of conforming to the uniform data standards of National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (CDEs) version 2.[14] Our primary aim was to examine IMPACT and CRASH model performance (calibration and discrimination) in this contemporary US cohort. The secondary aims included examination of model performance across TBI severities, age categories, and top enrolling sites.

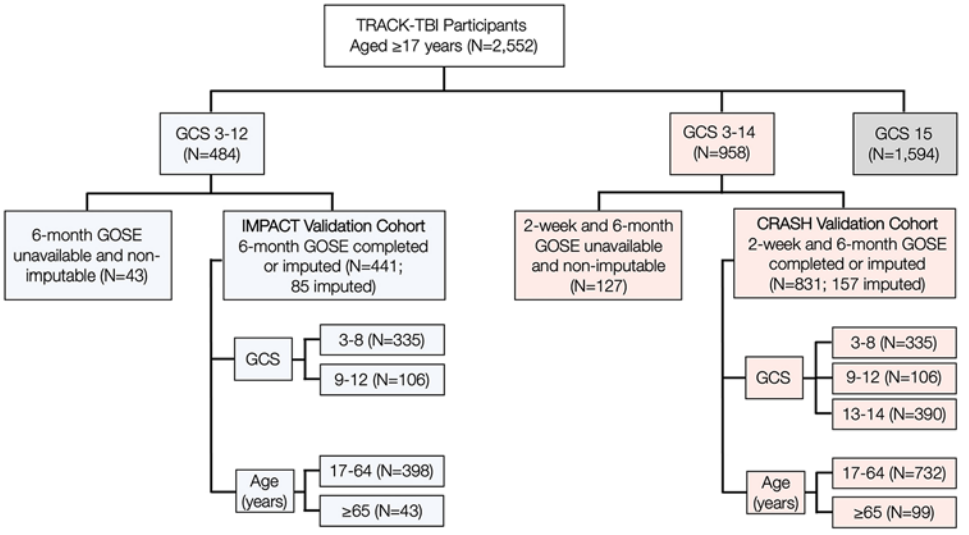

FIG. 1. CONSORT flow diagram of the included subjects. Figure is available in color online only.

Methods

Overview

The prospective observational TRACK-TBI study (ClinicalTrials.gov NCT02119182) enrolled patients through convenience sampling between February 2014 and July 2018. All subjects presented to the emergency department of participating centers, met the American Congress of Rehabilitation Medicine definition for TBI,[15] and received a clinically indicated noncontrast head CT within 24 hours of TBI. TRACK-TBI exclusion criteria included pregnancy, incarceration, nonsurvivable physical trauma, and pre-existing medical or neuropsychiatric conditions that could interfere with outcome assessments. Human subjects research conducted in this study followed the principles outlined in the Declaration of Helsinki. The institutional review board of each center approved all study protocols. Written informed consent was provided by the subject or their legally authorized representative before enrollment.

All data (demographic, clinical, neuroimaging, and outcomes) were collected in accordance with the NINDS TBI CDEs.[14,16] De-identified initial head CT scans were transmitted to a central imaging repository (Laboratory of Neuro Imaging) and coded to the neuroimaging CDEs[17] by a central board-certified neuroradiologist blinded to clinical data. Detailed study protocols are available at the TRACK-TBI study website.[13]

Outcome assessment was conducted using the Glasgow Outcome Scale–Extended (GOSE)[18] at 2 weeks, 3 months, 6 months, and 12 months, as previously described.[19] GOSE provides an 8-point ordinal measure of functional disability after TBI based on consciousness, independence, employability, social participation, and symptomatology, ranging from death (GOSE score 1) to recovery to preinjury status (GOSE score 8).[18] In TRACK-TBI, GOSE was administered through structured interviews by trained personnel in person or by telephone. The IMPACT and CRASH model definitions of mortality (GOSE score 1) and unfavorable outcome (GOSE score 1–4) were used for our study.[6]

Description of IMPACT and CRASH Models

Three levels of IMPACT models (Core, Extended, and Laboratory [Lab]) were developed from a database of 8509 acute TBI patients who presented with GCS score 3–12 from 8 randomized controlled trials and 3 observational studies conducted between 1984 and 1997.[6] IMPACT models evaluated predictors of 6-month mortality and unfavorable outcome. The Core model included age, GCS motor score, and pupillary reactivity as predictors; the Extended model added hypotension, hypoxia, Marshall CT score,[20] traumatic subarachnoid hemorrhage (tSAH), and epidural hematoma on initial head CT to the predictors from the Core model; and the Lab model added hemoglobin and glucose levels to the predictors from the Extended model (Supplementary Table 1).

Two levels of CRASH models (Basic and CT) were developed using the CRASH trial dataset of 10,008 TBI patients who presented within 8 hours of injury with GCS score 3–14.[5] Seventy-five percent of CRASH patients were from low- or middle-income countries. CRASH models evaluated predictors of 2-week mortality and 6-month unfavorable outcome. The Basic model included 4 predictors: age, GCS score, pupillary reactivity, and major extracranial injury. The CT model added initial head CT findings of petechial hemorrhage, obliteration of the third ventricle or basal cisterns, tSAH, midline shift, and nonevacuated hematoma (Supplementary Table 1).

Cohort Selection

For our primary aim, we evaluated the performances of all IMPACT and CRASH model levels. Evaluation of secondary aims utilized the most comprehensive level of each model (IMPACT-Lab and CRASH-CT) because laboratory and CT findings have been shown to improve model performance.[6,9,21]

The CONSORT flow diagram is shown in Fig. 1. Of 2552 TRACK-TBI subjects aged ≥ 17 years, those meeting the IMPACT and CRASH model criteria (for IMPACT, initial GCS score 3–12 and completed 6-month GOSE; for

TABLE 1. Discriminative abilities of the IMPACT and CRASH models

	IMPACT Models		
	Core	Extended	Lab
AUC for mortality at 6 mos			
Development*	0.77	0.81	0.79
External validation†	0.81 (0.76–0.86)	0.86 (0.82–0.90)	0.84 (0.79–0.88)
Case-mix corrected†	0.77 (0.74–0.80)	0.81 (0.78–0.83)	0.79 (0.77–0.82)
AUC for unfavorable outcome at 6 mos			
Development*	0.78	0.81	0.81
External validation†	0.78 (0.73–0.82)	0.82 (0.78–0.86)	0.83 (0.79–0.86)
Case-mix corrected†	0.77 (0.75–0.80)	0.81 (0.78–0.83)	0.81 (0.78–0.83)
	CRASH Models		
	Basic	CT	
AUC for mortality at 2 wks			
Development*	0.86	0.88	
External validation†	0.90 (0.85–0.93)	0.92 (0.88–0.94)	
Case-mix corrected†	0.90 (0.87–0.93)	0.91 (0.88–0.93)	
AUC for unfavorable outcome at 6 mos			
Development*	0.81	0.83	
External validation†	0.86 (0.83–0.89)	0.88 (0.86–0.91)	
Case-mix corrected†	0.83 (0.80–0.85)	0.83 (0.81–0.86)	

AUC = area under the receiver operating characteristic curve.
Mean AUC is shown with 95% CI in parentheses.
* Development AUC represents the mean AUC calculated in the original IMPACT or CRASH study.
† External validation and case-mix–corrected AUCs were calculated using the respective TRACK-TBI validation cohorts.

CRASH, initial GCS score 3–14, 2-week mortality data, and completed 6-month GOSE) were included in our analysis. Subjects without 2-week mortality or 6-month GOSE data but who completed GOSE at another study time point had their data imputed using the Markov multistate model developed by the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) investigators.[22] Subjects who did not complete GOSE at any time point were excluded. Clinical, laboratory, and CT data conforming to IMPACT and CRASH model criteria were extracted.[5,6] Missing predictor values were imputed using multiple imputation based on the predictors and outcomes included in the IMPACT and CRASH models using the "mice" package in R.[23]

Statistical Analysis

For our primary aim, the performances (calibration and discrimination) of the IMPACT and CRASH models were evaluated using the overall TRACK-TBI validation cohort. For our secondary aims, model performance analyses were stratified on the basis of TBI severity according to initial GCS score (severe [GCS score 3–8], moderate [9–12], and mild [13–14] for CRASH), age (17–64 years vs ≥ 65 years), and the 5 TRACK-TBI study sites with the highest enrollment (sites A–E) (individual sample sizes were not reported to maintain de-identification of the sites).

The IMPACT and CRASH logistic regression models were validated by applying the coefficients of the original models to the validation data. Model performance was assessed for calibration and discrimination. Calibration, representing overall agreement between predicted and observed outcome probabilities, was tested with the calibration slope and intercept. Observed frequencies of mortality and unfavorable outcome were plotted against model-predicted risk. Calibration slope and intercept were calculated for each model. A perfectly calibrated model would have a slope of 1, indicating that as predicted probabilities increase, observed event rates increase at the same rate. Intercept or calibration-in-the-large measures whether the predictions are systematically too high or too low. Ideally, the intercept is 0, indicating the observed event rate is 0 when the predicted probability is 0. A negative intercept and associated 95% CI suggest overestimation of predicted risks, and a positive intercept and 95% CI suggests underestimation. Model discrimination at external validation may be affected by the distribution of patient characteristics (case-mix) in the validation cohort. Therefore, case-mix–corrected area under the receiver operating characteristic curves were calculated to reflect model discrimination under the assumption that the regression coefficients are correct for the validation population, and these were provided as the c-statistic for the IMPACT and CRASH models when applied to the overall TRACK-TBI validation cohort. The c-statistics from the original IMPACT and CRASH studies,[5,24] and external validation and case-mix correction in our TRACK-TBI cohort, are provided in Table 1. Generally, a c-statistic of 0.5 suggests no discrimination, 0.7–0.8 is considered acceptable, 0.8–0.9 is considered good, and > 0.9, excellent.[25] Associations between the predictors and outcome measures in each model were reported as ORs; 95% CIs were provided for calibration intercepts, slopes, and c-statistics. Statistical significance was assessed at p

TABLE 2. Descriptive characteristics of the TRACK-TBI validation cohort compared across 6-month mortality (GOSE score 1 vs 2–8) and 6-month unfavorable (GOSE 1–4 vs 5–8) outcomes using the IMPACT-Lab model

		6-mo GOSE					
	Overall	GOSE Score 1	GOSE Score 2–8	p Value	GOSE Score 1–4	GOSE Score 5–8	p Value
Age							
17–64 yrs	398 (90.25)	59 (68.6)	339 (95.49)	<0.0001	178 (82.41)	220 (97.78)	<0.0001
≥65 yrs	43 (9.75)	27 (31.4)	16 (4.51)		38 (17.59)	5 (2.22)	
Overall	441 (100)	86 (100)	365 (100)		216 (100)	225 (100)	
GCS total score							
9–12	106 (24.04)	59 (10.47)	97 (27.32)	0.0007	37 (17.13)	69 (30.67)	0.0012
3–8	335 (75.96)	77 (89.53)	258 (72.68)		179 (82.87)	156 (69.33)	
Overall	441 (100)	86 (100)	365 (100)		216 (100)	225 (100)	
GCS motor score							
5/6	138 (31.58)	14 (16.28)	124 (35.33)	0.0040	46 (21.5)	92 (41.26)	0.0005
4	65 (14.87)	12 (13.95)	53 (15.1)		28 (13.08)	37 (16.59)	
3	17 (3.89)	2 (2.33)	15 (4.27)		8 (3.74)	9 (4.04)	
2	26 (5.95)	8 (9.3)	18 (5.13)		17 (7.94)	9 (4.04)	
1	191 (43.71)	50 (58.14)	141 (40.17)		115 (53.74)	76 (34.08)	
Overall	437 (100)	86 (100)	351 (100)		214 (100)	223 (100)	
Pupillary reactivity							
Both reactive	279 (70.45)	30 (38.46)	249 (78.3)	0.0005	108 (56.25)	171 (83.82)	0.0005
1 reactive	29 (7.32)	12 (15.38)	17 (5.35)		20 (10.42)	9 (4.41)	
None reactive	88 (22.22)	36 (46.15)	52 (16.35)		64 (33.33)	24 (11.76)	
Overall	396 (100)	78 (100)	318 (100)		192 (100)	204 (100)	
Hypotension							
No	387 (87.76)	71 (82.56)	316 (89.01)	0.1405	179 (82.87)	208 (92.44)	0.0023
Yes	54 (12.24)	15 (17.44)	39 (10.99)		37 (17.13)	17 (7.56)	
Overall	441 (100)	86 (100)	355 (100)		216 (100)	225 (100)	
Hypoxia							
No	374 (84.81)	71 (82.56)	303 (85.35)	0.5061	175 (81.02)	199 (88.44)	0.0338
Yes	67 (15.19)	15 (17.44)	52 (14.65)		41 (18.98)	26 (11.56)	
Overall	441 (100)	86 (100)	355 (100)		216 (100)	225 (100)	
Marshall CT classification							
I	30 (7.39)	0 (0)	30 (9.04)	0.0005	1 (0.52)	29 (13.55)	0.0005
II	177 (43.6)	15 (20.27)	62 (48.8)		71 (36.98)	106 (49.53)	
III/IV	41 (10.1)	10 (13.51)	31 (9.34)		20 (10.42)	21 (9.81)	
V/VI	158 (38.92)	49 (66.22)	109 (32.83)		100 (52.08)	58 (27.1)	
Overall	406 (100)	74 (100)	332 (100)		192 (100)	214 (100)	
Epidural hematoma							
No	339 (83.5)	69 (93.24)	270 (81.33)	0.0142	168 (87.5)	171 (79.91)	0.0448
Yes	67 (16.5)	5 (6.76)	62 (18.67)		24 (12.5)	43 (20.09)	
Overall	406 (100)	74 (100)	332 (100)		192 (100)	214 (100)	
tSAH							
No	91 (22.41)	4 (5.41)	87 (26.2)	<0.0001	20 (10.42)	71 (33.18)	<0.0001
Yes	315 (77.59)	70 (94.59)	245 (73.8)		172 (89.58)	143 (66.82)	
Overall	406 (100)	74 (100)	332 (100)		192 (100)	214 (100)	

Values are shown as number (%) unless indicated otherwise.

< 0.05. Analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing).

Results

Demographic and Clinical Characteristics

Overall, 441 TRACK-TBI subjects met the inclusion criteria for IMPACT and 831 met the criteria for CRASH. Subject characteristics and univariate comparisons for IMPACT and CRASH validation cohorts are shown in Tables 2 and 3, respectively. In the IMPACT cohort, 335 (76.0%) had severe TBI (GCS score 3–8) and 106 had moderate TBI (GCS score 9–12). The majority were aged 17–64 years (n = 398 [90.2%]) and 43 (9.8%) were ≥ 65 years. At 6 months, 86 (19.5%) had died and 216 (49.0%) had unfavorable outcome. IMPACT predictors[24] independently associated with higher risk of mortality in the TRACK-TBI cohort included older age, abnormal

TABLE 3. Descriptive characteristics of the TRACK-TBI validation cohort compared across 2-week mortality (GOSE score 1 vs 2–8) and 6-month unfavorable (GOSE 1–4 vs 5–8) outcome using the CRASH-CT model

		2-wk GOSE			6-mo GOSE		
	Overall	GOSE Score 1	GOSE Score 2–8	p Value	GOSE Score 1–4	GOSE Score 5–8	p Value
Age							
17–64 yrs	732 (88.09)	43 (58.11)	689 (91.02)	<0.0001	192 (78.69)	540 (91.99)	<0.0001
≥65 yrs	99 (11.91)	31 (41.89)	68 (8.98)		52 (21.31)	47 (8.01)	
Overall	831 (100)	74 (100)	757 (100)		244 (100)	587 (100)	
GCS total score							
13–14	390 (46.93)	9 (12.16)	381 (50.33)		28 (11.48)	362 (61.67)	
9–12	106 (12.76)	4 (5.41)	102 (13.47)	0.0005	37 (15.16)	69 (11.75)	0.0005
3–8	335 (40.31)	61 (82.43)	274 (36.2)		179 (73.36)	156 (26.58)	
Overall	831 (100)	74 (100)	757 (100)		244 (100)	587 (100)	
Pupillary reactivity							
Both reactive	622 (83.71)	26 (39.39)	596 (88.04)		131 (60.65)	491 (93.17)	
1 reactive	32 (4.31)	10 (15.15)	22 (3.25)	0.0005	21 (9.72)	11 (2.09)	0.0005
None reactive	89 (11.98)	30 (45.45)	59 (8.71)		64 (29.63)	25 (4.74)	
Overall	743 (100)	66 (100)	677 (100)		216 (100)	527 (100)	
Major extracranial injury							
No	631 (75.93)	52 (70.27)	579 (76.49)	0.2543	158 (64.75)	473 (80.58)	<0.0001
Yes	200 (24.07)	22 (29.73)	178 (23.51)		86 (35.25)	114 (19.42)	
Overall	831 (100)	86 (100)	757 (100)		244 (100)	587 (100)	
tSAH							
No	327 (41.71)	5 (7.81)	322 (44.72)		27 (12.33)	300 (53.1)	
Yes	457 (58.29)	59 (92.19)	398 (55.28)	<0.0001	192 (87.67)	265 (46.9)	<0.0001
Overall	784 (100)	64 (100)	720 (100)		219 (100)	565 (100)	
Petechial hemorrhage							
No	647 (82.53)	48 (75)	599 (83.19)	0.1202	153 (69.86)	494 (87.43)	<0.0001
Yes	137 (17.47)	16 (25)	121 (16.81)		66 (30.14)	71 (12.57)	
Overall	784 (100)	64 (100)	720 (100)		219 (100)	565 (100)	
Obliteration of 3rd ventricle or basal cisterns							
No	722 (92.09)	33 (51.56)	689 (95.69)	<0.0001	165 (75.34)	557 (98.58)	<0.0001
Yes	62 (7.91)	31 (48.44)	31 (4.31)		54 (24.66)	8 (1.42)	
Overall	784 (100)	64 (100)	720 (100)		219 (100)	565 (100)	
Midline shift							
No	684 (87.24)	33 (51.56)	651 (90.42)	<0.0001	153 (69.86)	531 (93.98)	<0.0001
Yes	100 (12.76)	31 (48.44)	69 (9.58)		66 (30.14)	34 (6.02)	
Overall	784 (100)	64 (100)	720 (100)		219 (100)	565 (100)	
Nonevacuated hematoma							
No	769 (98.09)	54 (84.38)	715 (99.31)	<0.0001	207 (94.52)	562 (99.47)	<0.0001
Yes	15 (1.91)	10 (15.62)	5 (0.69)		12 (5.48)	3 (0.53)	
Overall	784 (100)	64 (100)	720 (100)		219 (100)	565 (100)	

Values are shown as number (%) unless indicated otherwise.

pupillary reactivity, hypotension, and Marshall score ≥ 3; predictors of unfavorable outcome included older age, lower GCS motor score, unreactive pupils, hypotension, Marshall score ≥ 5, tSAH, and lower hemoglobin (Supplementary Table 2). Epidural hematoma was associated with decreased risk of mortality and unfavorable outcome. Hypoxia, tSAH, glucose level, and hemoglobin level did not significantly predict mortality, and hypoxia and glucose level did not significantly predict unfavorable outcome.

In the CRASH validation cohort, 335 subjects (40.3%) had severe TBI, 106 (12.8%) had moderate, and 390 (46.9%) had mild. The majority were aged 17–64 years (n = 732 [88.1%]) and 99 were ≥ 65 years (11.9%). Seventy-four (8.9%) subjects had 2-week mortality data and 244 (29.4%) had 6-month unfavorable outcome data. CRASH predictors[5] independently associated with higher risk of mortality in the TRACK-TBI study included older age, lower GCS score, abnormal pupillary reactivity, and compression of third ventricle or basal cisterns; predictors of unfavorable outcome were older age, lower GCS score, unreactive pupils, petechial hemorrhage, third ventricular/basal cistern compression, and tSAH (Supplementary Table 3). Petechial hemorrhage and tSAH did not significantly predict mortality, and extracranial injury, midline

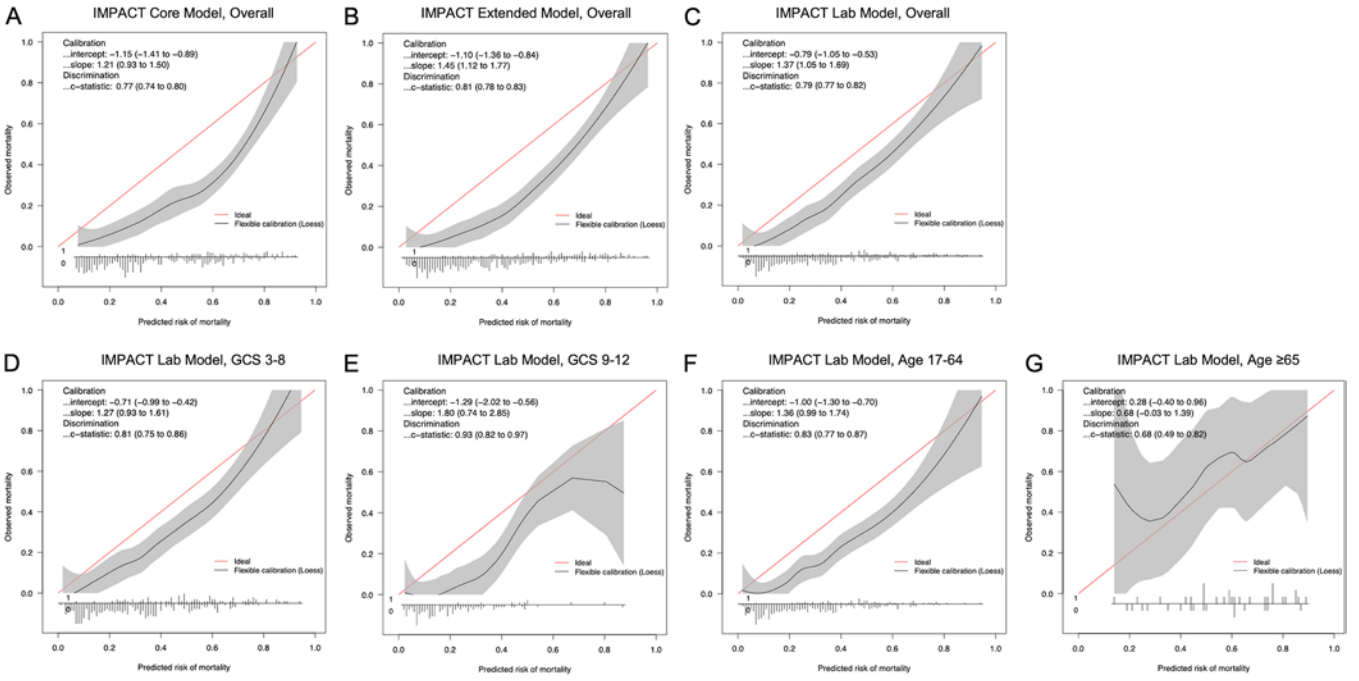

FIG. 2. Prediction of mortality in the overall cohort, stratified by GCS score and age, using the IMPACT models. Calibration plots for prediction of 6-month mortality in the overall TRACK-TBI validation cohort are shown for the IMPACT Core (n = 441) (**A**), Extended (n = 441) (**B**), and Lab (n = 441) (**C**) models. Stratified analyses using the IMPACT-Lab model are shown for TBI severity (GCS score 3–8 [n = 335] [**D**] and GCS score 9–12 [n = 106] [**E**]) and age (17–64 years [n = 398] [**F**] and ≥ 65 years [n = 43] [**G**]). The ideal reference line in *red* represents perfect model calibration with slope = 1 and intercept = 0. Estimated model calibration with LOESS smoothing is shown as the *black curved line* in each plot. The intercept, slope, and c-statistic of model calibration are shown with 95% CIs in the *top left corner of each plot*, and 95% CIs are shaded in *gray* on the plot. Figure is available in color online only.

shift, and nonevacuated hematoma did not significantly predict mortality or unfavorable outcome.

Performance of IMPACT Models: Mortality

The Core, Extended, and Lab models showed good discrimination of mortality (case-mix–corrected c-statistics 0.81, 0.86, and 0.84, respectively) (Table 1). Calibration analyses showed that all models overpredicted mortality in the overall cohort (Fig. 2A–C). The Lab model had intercept −0.79 (95% CI −1.05 to −0.53) and slope 1.37 (1.05–1.69) in TRACK-TBI.

Stratified on the basis of TBI severity, discrimination remained good using the Lab model (c-statistic for GCS score 3–8, 0.81 [95% CI 0.75–0.86]; GCS score 9–12, 0.93 [0.82–0.97]). Mortality remained overpredicted in both cohorts (intercept −0.71 [−0.99 to −0.42] and intercept −1.29 [−2.02 to −0.56], respectively) (Fig. 2D and E). The model appeared to better predict mortality in patients with GCS score 3–8 compared to those with GCS score 9–12. Stratified on the basis of age, the model had good discrimination and overpredicted mortality in younger adults (intercept −1.00 [−1.30 to −0.70], slope 1.36 [0.99–1.74], c-statistic 0.83 [0.77–0.87]) (Fig. 2F) and was inconclusive in older adults due to wide CIs for intercept, slope, and c-statistic (Fig. 2G).

Calibration differences were observed across the 5 top enrolling sites, while discrimination was adequate to good across sites (c-statistic 0.79–0.84). The intercepts and CIs for the top 3 enrolling sites remained negative (Supplementary Fig. 1A, B, and D), suggesting overprediction of mortality, while the CIs were wider and traversed 0 for the other 2 sites (Supplementary Fig. 1C and E), suggesting that mortality may be as predicted at these sites and/or limited by small sample sizes. Slopes showed variability and sinusoidal patterns across sites, again suggesting limitations in interpretation due to small sample size.

Performance of IMPACT Models: Unfavorable Outcome

Discriminative ability for unfavorable outcome improved with model complexity (case-mix–corrected c-statistic for the Core model was 0.78; Extended model, 0.82; Lab model, 0.83) (Table 1). Calibration performance was similar across the 3 models (intercept −0.12 to 0.07, slope 1.09–1.21), and observed unfavorable outcome was similar to predicted (Fig. 3A–C).

The calibration performance of the Lab model was comparable when stratified on the basis of TBI severity and better in patients with GCS score 3–8 (intercept 0.10 [95% CI −0.15 to 0.35]), slope 1.10 [0.85–1.36], and c-statistic 0.81 [0.76–0.85]) compared to patients with GCS score 9–12 (intercept −0.01 [−0.46 to 0.44], slope 1.61 [0.98–2.25], and c-statistic 0.86 [0.77–0.92]); narrower CIs in the former suggest that performance may be related to sample size (Fig. 3D and E). Stratified on the basis of age, the model performed well in younger adults (intercept 0.02 [−0.21 to 0.25], slope 1.21 [0.95–1.46], and c-statistic 0.82 [0.77–0.86]) (Fig. 3F). In older adults, discrimination was less robust (c-statistic 0.62 [0.43–

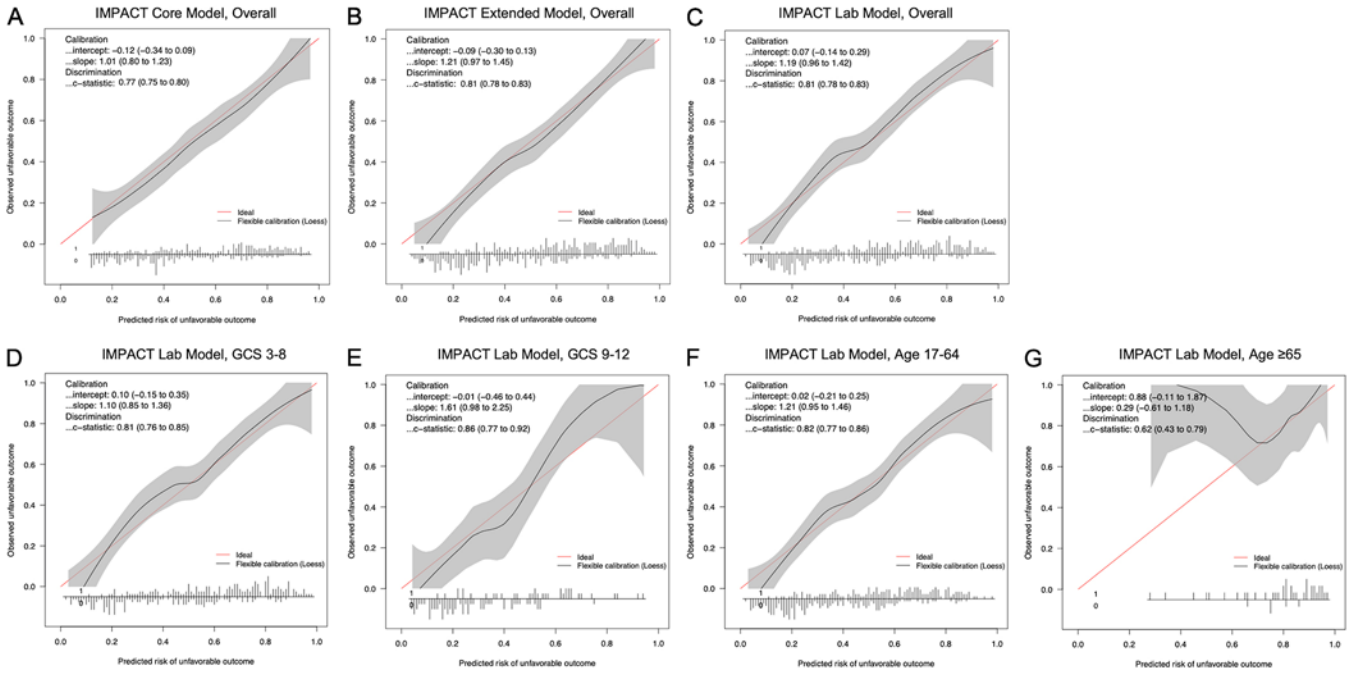

FIG. 3. Prediction of unfavorable outcome in the overall cohort, stratified by GCS score and age, using IMPACT models. Calibration plots for prediction of 6-month unfavorable outcome (GOSE score 1–4) in the overall TRACK-TBI validation cohort are shown for the IMPACT Core (**A**), Extended (**B**), and Lab (**C**) models. Stratified analyses using the IMPACT-Lab model are shown for TBI severity (GCS score 3–8 [**D**] and GCS score 9–12 [**E**]) and age (17–64 years [**F**] and ≥ 65 years [**G**]). The intercept, slope, and c-statistic of model calibration are shown with 95% CIs in the *top left corner of each plot*, and 95% CIs are shaded in *gray* on the plot. Cohort sizes (n) for each panel are the same as those reported in Fig. 2. Figure is available in color online only.

0.79]); calibration analyses showed acceptable prediction in subjects with predicted risk > 0.7, and underprediction with wide CIs (limited interpretability) in those with predicted risk < 0.7 (Fig. 3G).

Across the leading enrollment sites, the Lab model had good discrimination (c-statistic 0.81–0.91). Calibration analyses showed acceptable prediction of unfavorable outcome across individual sites (Supplementary Fig. 2A–E).

Performance of CRASH Models: Mortality

The Basic and CT models showed excellent case-mix–corrected discrimination (c-statistics 0.90 and 0.92, respectively) (Table 1). The Basic model acceptably predicted overall 2-week mortality (intercept –0.04 [95% CI –0.32 to 0.23], slope 1.08 [0.87–1.29]) (Fig. 4A), whereas the CT model overpredicted mortality (intercept –1.06 [–1.36 to –0.75], slope 0.96 [0.79–1.14]) (Fig. 4B).

Stratified on the basis of TBI severity, the CRASH-CT model showed good discrimination with c-statistics 0.86, 0.98, and 0.89 for patients with GCS scores 3–8, 9–12, and 13–14, respectively. The model overpredicted mortality in patients with GCS score 3–8 (intercept –1.12 [95% CI –1.47 to –0.77], slope 0.91 [0.68–1.13]) and GCS score 9–12 (intercept –1.22 [–2.32 to –0.11], slope 1.60 [0.55–2.65]) and acceptably predicted mortality in patients with GCS score 13–14 (intercept –0.68 [–1.38 to 0.01], slope 1.33 [0.73–1.94]) (Fig. 4C–E). Stratified on the basis of age, the CT model showed good discrimination of mortality in both cohorts (c-statistics 0.91 and 0.87, respectively). The model overpredicted mortality in younger subjects (intercept –1.28 [–1.65 to –0.91], slope 0.93 [0.72–1.14]) (Fig. 4F) and showed a nonlinear relationship in older subjects (Fig. 4G).

At the leading enrolling sites, the CT model showed good to excellent discrimination of mortality (c-statistics 0.83–0.97), overpredicted mortality at sites A, B, and D, and acceptably predicted mortality at sites C and E. Calibration performance varied significantly between sites, with intercepts of –1.81 to –0.67 and slopes of 0.67 to 1.56 (Supplementary Fig. 3A–E).

Performance of CRASH Models: Unfavorable Outcome

The Basic and CT models showed good case-mix–corrected discrimination for unfavorable outcome (c-statistics 0.86 and 0.88, respectively) in the overall cohort (Table 1). The Basic model acceptably predicted unfavorable outcome (intercept –0.05 [95% CI –0.23 to 0.13], slope 1.16 [1.00–1.33]) (Fig. 5A), whereas the CT model overpredicted unfavorable outcome (intercept –0.60 [–0.78 to –0.41], slope 1.20 [1.03–1.37]) (Fig. 5B).

Stratified on the basis of TBI severity, discrimination was adequate to good across cohorts (c-statistics 0.81, 0.88, and 0.78 for patients with GCS scores 3–8, 9–12, and 13–15, respectively). The CT model overpredicted unfavorable outcome for GCS score 3–8 (intercept –0.45 [95% CI –0.70 to –0.20], slope 1.09 [0.83–1.35]) and GCS score 13–14 (intercept –1.35 [–1.77 to –0.94], slope 1.03 [0.68–1.38]); for GCS score 9–12, calibration was nonlinear (Fig. 5C–E).

The model displayed similar discrimination for both

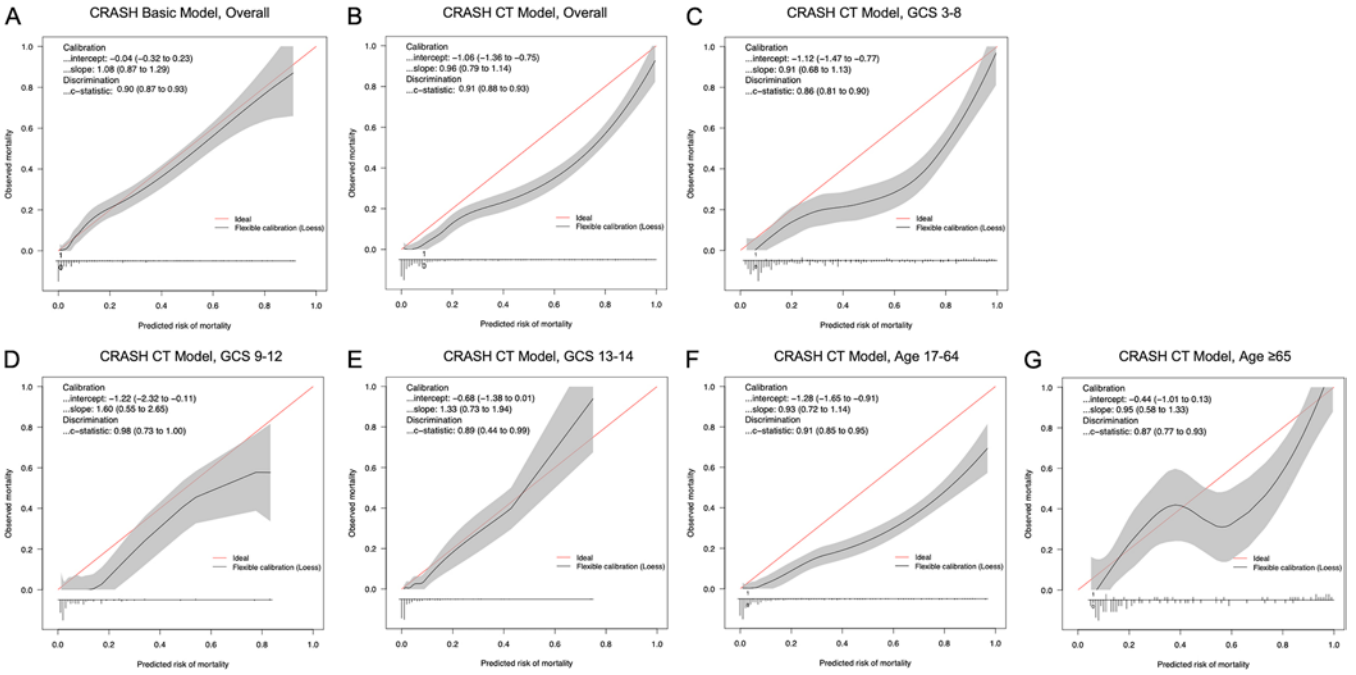

FIG. 4. Prediction of mortality in the overall cohort, stratified by GCS score and age, using CRASH models. Calibration plots for prediction of 2-week mortality in the overall TRACK-TBI validation cohort are shown for the CRASH-Basic (n = 831) (**A**) and CRASH-CT (n = 831) models (**B**). Stratified analyses using the CRASH-CT model are shown for TBI severity (GCS score 3–8 [n = 335] (**C**), GCS score 9–12 [n = 106] [**D**], and GCS score 13–14 [n = 390] [**E**]) and age (17–64 years [n = 732] [**F**] and ≥ 65 years [n = 99] [**G**]). The intercept, slope, and c-statistic of model calibration are shown with 95% CIs in the *top left corner of each plot*, and 95% CIs are shaded in *gray* on the plot. Figure is available in color online only.

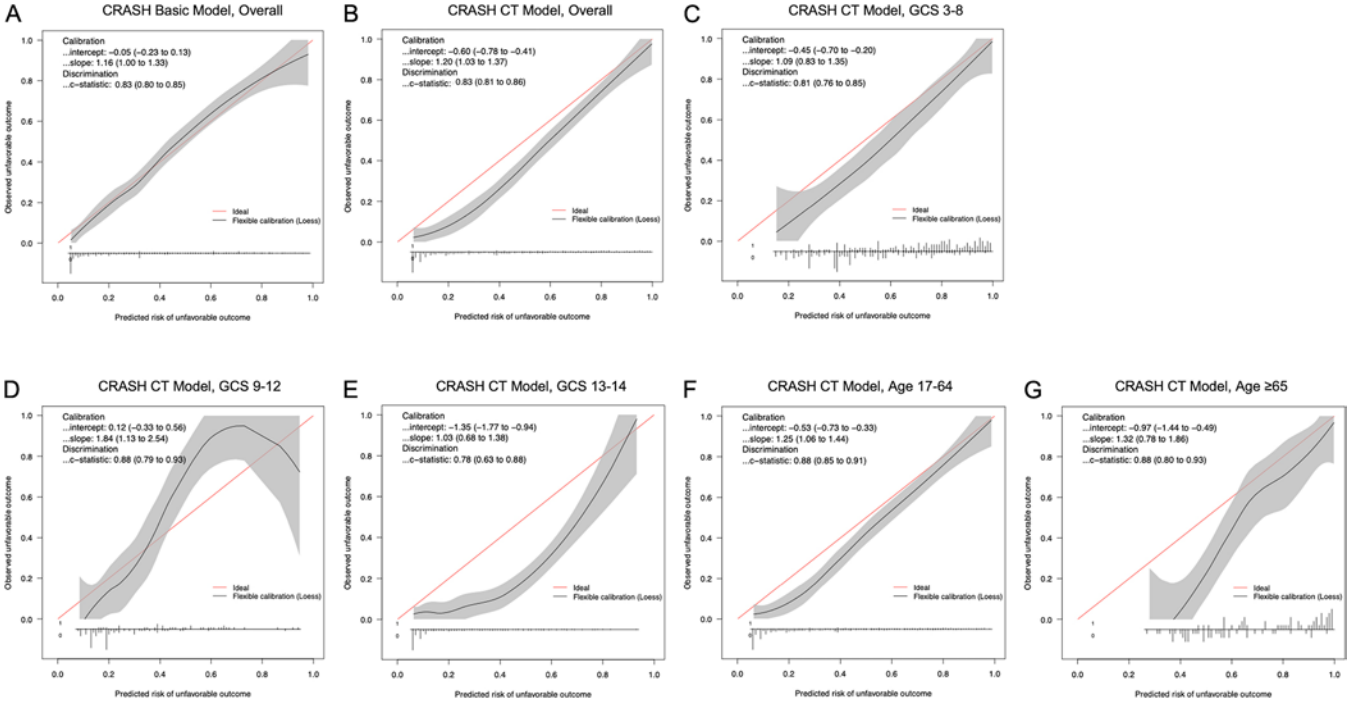

FIG. 5. Prediction of unfavorable outcome in the overall cohort, stratified by GCS score and age cohorts, using CRASH models. Calibration plots for prediction of 6-month unfavorable outcome (GOSE score 1–4) in the overall TRACK-TBI validation cohort are shown for the CRASH-Basic (**A**) and CRASH-CT (**B**) models. Stratified analyses using the CRASH-CT model are shown for TBI severity (GCS score 3–8 [**C**], GCS score 9–12 [**D**], and GCS 13–14 [**E**]) and age (17–64 years [**F**] and ≥ 65 years [**G**]). The intercept, slope, and c-statistic of model calibration are shown with 95% CIs in the *top left corner of each plot*, and 95% CIs are shaded in *gray* on the plot. Cohort sizes (n) for each panel are the same as those reported in Fig. 4. Figure is available in color online only.

age cohorts with c-statistics of 0.88 each. The model overpredicted unfavorable outcome in both cohorts (17–64 years, intercept −0.53 [95% CI −0.73 to −0.33] and slope 1.25 [1.06–1.44]; ≥ 65 years, intercept −0.97 [−1.44 to −0.49] and slope 1.32 [0.78–1.86]) (Fig. 5F and G).

Across the top enrolling sites, c-statistics for unfavorable outcome were good to excellent (0.85–0.92). Overprediction of unfavorable outcome was observed at sites B–E, whereas outcome was as predicted at site A (Supplementary Fig. 4A–E). Slopes at all sites traversed 1.

Discussion

Summary and Overall Model Performances

In this study, we externally validated the IMPACT and CRASH prognostic models using a contemporary multicenter cohort of US TBI patients. The IMPACT and CRASH models showed good discrimination of mortality and unfavorable outcomes in the overall TRACK-TBI cohort with c-statistics 0.84 and 0.83, respectively, for IMPACT and 0.92 and 0.88 for CRASH. Calibration analyses showed that the IMPACT and CRASH models overpredicted mortality, and CRASH overpredicted unfavorable outcome. Our results also highlighted the variability in model performance when stratified on the basis of TBI severity, older versus younger age, and study sites. We discuss potential factors that may explain these differences in performance and provide suggestions for further refinement of TBI prognostic models.

Effect of TBI Severity on Model Prediction

We noted several interesting observations when assessing model performance based on TBI severity. Firstly, the IMPACT-Lab and CRASH-CT models overpredicted mortality in the overall cohort and for patients with severe or moderate TBI. This suggests the presence of predictors in contemporary TBI care that were not accounted for by these models, which were developed using data from over 2 decades ago. Candidate factors, modifiers, and predictors implicate the many advancements in TBI care since the early 2000s, including updated surgical and neurocritical care guidelines,[26–28] improved evaluation and management of clinical data (e.g., dashboards, rapid order processing using electronic medical records), expedited time to surgery and technological capabilities of the modern surgical suite, and the multidisciplinary approach to neurotrauma care at US level I trauma centers, all of which may have contributed to reductions in observed versus predicted mortality. Secondly, the CRASH-CT model acceptably predicted mortality and overestimated unfavorable outcome for mild TBI patients in TRACK-TBI, denoting that mild TBI patients who survived tended to have better outcomes than predicted. One explanation may be the improved understanding and awareness of mild TBI pathophysiology, management, subacute and chronic sequelae, and their appropriate follow-up strategies,[1] and moreover, differences in the availabilities of rehabilitation and long-term follow-up to TRACK-TBI patients compared to the historical CRASH cohort, of whom a majority were from low- or middle-income countries.[5] Thirdly, while the observed unfavorable outcome was as predicted for moderate TBI according to the CRASH-CT model, the calibration plot showed a sinusoidal pattern that was different from the patterns of severe and mild TBI. The smaller sample size of the moderate TBI subgroup (relative to severe and mild TBI), as well as the heterogeneity of the clinical characteristics seen in moderate TBI patients,[29,30] may have contributed to these observed differences.

Taken together with prior claims,[1,31,32] our results implicate the need for more accurate and more clinically relevant assessment of TBI severity beyond the GCS, which would likely improve model performance. We propose the evaluation of acute neuroimaging findings, including intracranial lesion types, locations, and quantifiable volumes, for TBI severity classification and prognostication.[19,33,34] Overall, our results underscore the need for continuous refinement of prognostic models to account for evolving TBI care measures and up-to-date patient data.

Effect of Age on Model Prediction

We found differences in mortality prediction between patients aged 17–64 years and those ≥ 65 years by using the IMPACT and CRASH models, with mortality overestimated in younger adults and generally as estimated in older adults with increased variability. Although older age remained a significant predictor of mortality and unfavorable outcome in the TRACK-TBI cohort on multivariable regressions, calibrations for the older cohort had a wide CI due to small sample sizes. Possible explanations include factors such as frailty and medical morbidities, which may contribute to increased mortality risk and worse outcomes in elderly patients.[35,36] Interpretive caution should be used when applying historical models to older TBI patients, and investigations to determine predictors specific to outcomes after elderly TBI are needed to develop accurate prognostic models in this population.

Site-Specific Differences in Model Performance

Our findings that IMPACT and CRASH model calibration for mortality varied between TRACK-TBI sites may be explained by differences in sample size, case-mix, and center-specific therapies and protocols such as predilection for surgical intervention, intracranial neuromonitoring placement, and withdrawal of life support treatment. These site-specific differences underscore the importance for validating models using contemporary, multicenter data and impel the need for further examination of center-specific patient demographic characteristics and care practices[37,38] that may drive differences in outcomes between sites.

Comparison With the CENTER-TBI Validation Cohort

A 2021 CENTER-TBI study assessed IMPACT and CRASH model performances using 1173 and 1742 patients, respectively, from 59 centers in 18 countries across Europe and Israel.[39] IMPACT and CRASH model performances for mortality and unfavorable outcome were similar between TRACK-TBI and CENTER-TBI. The IMPACT models overpredicted mortality in both validation cohorts while reasonably estimating unfavorable outcome. The CRASH-CT model overpredicted mortality

and unfavorable outcome in both studies. Taken together, these studies indicate that IMPACT and CRASH models perform reasonably well overall in contemporary US and European settings. However, the discrepancies observed between predicted versus observed outcomes in both studies strongly suggest the need for revising these models with up-to-date predictors to improve their prognostic accuracy.

Future Directions for Improving TBI Prognostic Models

Taken together, our study advocates for more in-depth investigations of several potential factors to improve prognostic modeling of TBI patients. CNS-specific blood-based biomarkers, with glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1 at the forefront, have been widely studied for their diagnostic utility in detecting intracranial injury on neuroimaging and are associated with TBI severity and prognosis.[40] The use of MRI to improve detection and characterization of intracranial lesion types has been shown to improve TBI prognostic models.[33] As our understanding of TBI pathogenesis continues to reveal the heterogeneity and complexity inherent to this disease process, improved assessment of TBI severity beyond the GCS will benefit prognostication.[1] Accordingly, CNS-specific blood-based biomarkers, neuroimaging features and lesion volumetrics, and frailty should be considered when refining prognostic models.

Characterization of bio-psycho-socio-ecological (BPSE) variables may provide a more comprehensive picture of the factors affecting recovery.[1] Incorporation of these variables into prognostic models could improve model performance and accuracy, particularly for mild TBI because BPSE factors may predominate and affect recovery.[41] Notably, the outcome range defined as "unfavorable" during development of the IMPACT and CRASH models may not necessarily be considered "unfavorable" for an individual patient or family, e.g., a patient with GOSE score 4 may have the ability to be home alone safely for up to 24 hours, allowing caregivers to be gainfully employed and augment economic sufficiency. Recent evidence has shown that moderate to severe TBI patients may continue to improve beyond 2 years after injury.[42,43] Data coding and curation efforts to capture intracranial injury location, volume, and progression are in process within the TRACK-TBI consortium; when data become available, they will be applied toward improving future prognostic models. Lastly, our findings of overprediction of mortality and unfavorable outcome, and discrepant model performances across severity, age, and institution-specific subgroups, should inform the design of endpoints, targeted populations, and treatment variables in future TBI clinical trials.

Limitations

We recognize several limitations. Although we aimed to validate the IMPACT and CRASH models in the US population, TRACK-TBI enrolled subjects through convenience sampling at level I trauma centers, which may not be representative of other US populations or areas with limited resources. Discrepancies in the observed model performances in our study may be related to subtle differences in inclusion criteria between the TRACK-TBI and original IMPACT/CRASH studies. Understanding of the appropriate use and limitations of the GOSE have evolved over time,[44] which may affect the accuracy of applying historical models to contemporary cohorts. To overcome the limitation of variable missingness and loss to follow-up inherent to large observational studies, we applied the validated Markov multistate model method from CENTER-TBI to impute GOSE data for 19% of our cohort.[22] However, imputation does not replace the true accuracy of a collected data point. Additionally, we focused on assessing the performance of the most comprehensive models (IMPACT-Lab and CRASH-CT). Although many suspected TBI patients are considered for CT, some may not receive laboratory evaluations; thus, these complex models may not be realistically applicable to all patients in the practice setting. With the shift toward data-driven medicine,[45] it is worth emphasizing that although prognostic models can aid medical decision-making, they should be utilized as a guide and not used as the primary justification for implementing or withholding interventions. The tendency of IMPACT/CRASH models to overestimate mortality and poorer outcomes indicate the need for their refinement to augment clinical utility.

Conclusions

IMPACT and CRASH models adequately discriminated mortality and unfavorable outcome. The observed overestimations of mortality and unfavorable outcome underscore the need to update prognostic models in order to incorporate contemporary changes in TBI management and case-mix. Investigations to elucidate the relationships between increased survival, outcome, treatment intensity, and site-specific practices will be highly relevant to construct updated models in specific TBI subpopulations (e.g., older adults, those with moderate TBI), which may benefit from the inclusion of blood-based biomarkers, neuroimaging features, and treatment data.

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Appendix

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Disclosures

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Supplemental Information

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