Outcome prediction after moderate and severe traumatic brain injury: external validation of two established prognostic models in 1742 European patients

Dijkland, S.A.; Helmrich, I.R.A.R.; Nieboer, D.; Jagt, M. van der; Dippel, D.W.J.; Menon, D.K.; ... ; CENTER-TBI Participants Investig

JOURNAL OF NEUROTRAUMA 38:1377–1388 (May 15, 2021)

DOI: 10.1089/neu.2020.7300

Outcome Prediction after Moderate and Severe Traumatic Brain Injury: External Validation of Two Established Prognostic Models in 1742 European Patients

Simone A. Dijkland,[1] Isabel R.A. Retel Helmrich,[1] Daan Nieboer,[1] Mathieu van der Jagt,[2] Diederik W.J. Dippel,[3] David K. Menon,[4] Nino Stocchetti,[5,6] Andrew I.R. Maas,[7] Hester F. Lingsma,[1] Ewout W. Steyerberg[1,8]; and the CENTER-TBI Participants and Investigators*

Abstract

The International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models predict functional outcome after moderate and severe traumatic brain injury (TBI). We aimed to assess their performance in a contemporary cohort of patients across Europe. The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core study is a prospective, observational cohort study in patients presenting with TBI and an indication for brain computed tomography. The CENTER-TBI core cohort consists of 4509 TBI patients available for analyses from 59 centers in 18 countries across Europe and Israel. The IMPACT validation cohort included 1173 patients with GCS ≤12, age ≥14, and 6-month Glasgow Outcome Scale-Extended (GOSE) available. The CRASH validation cohort contained 1742 patients with GCS ≤14, age ≥16, and 14-day mortality or 6-month GOSE available. Performance of the three IMPACT and two CRASH model variants was assessed with discrimination (area under the receiver operating characteristic curve; AUC) and calibration (comparison of observed vs. predicted outcome rates). For IMPACT, model discrimination was good, with AUCs ranging between 0.77 and 0.85 in 1173 patients and between 0.80 and 0.88 in the broader CRASH selection ($n = 1742$). For CRASH, AUCs ranged between 0.82 and 0.88 in 1742 patients and between 0.66 and 0.80 in the stricter IMPACT selection ($n = 1173$). Calibration of the IMPACT and CRASH models was generally moderate, with calibration-in-the-large and calibration slopes ranging between −2.02 and 0.61 and between 0.48 and 1.39, respectively. The IMPACT and CRASH models adequately identify patients at high risk for mortality or unfavorable outcome, which supports their use in research settings and for benchmarking in the context of quality-of-care assessment.

Keywords: clinical prediction model; external validation; outcome; prognosis; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a heterogeneous disease with substantial variation in trauma mechanisms, pathophysiology, and clinical presentation.[1] Early outcome prediction is important in research settings (e.g., for selecting patients for clinical trials).[2] Informed predictions could also facilitate risk communication with patients or relatives and case-mix adjustment for benchmarking quality of care.[3] Many prognostic models for functional outcome after moderate and severe TBI have been developed and validated.[4–6] Of these, the International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) models and the Corticoid Randomisation After Significant Head injury (CRASH) models are the most widely known.[7,8]

[1]Department of Public Health, Center for Medical Decision Making, [2]Department of Intensive Care, [3]Department of Neurology, Erasmus MC-University Medical Center, Rotterdam, the Netherlands.
[4]Division of Anesthesia, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom.
[5]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.
[6]Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Department of Anesthesia and Critical Care, Neuroscience Intensive Care Unit, Milan, Italy.
[7]Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium.
[8]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands.
*The CENTER-TBI Participants and Investigators are listed at end of the article.

These models were developed a decade ago on large, multicenter cohorts using state-of-the-art statistical methodology. The models combine clinical, radiological, and laboratory admission characteristics to predict risk of mortality and unfavorable outcome. The IMPACT and CRASH models have shown highly variable model performance across different settings.[4] Moreover, previous validation studies were mostly performed in small observational cohorts or randomized clinical trials (RCTs) that may not represent the current TBI population. We aimed to gain insight in the performance of the IMPACT and CRASH prognostic models in contemporary patients across Europe.

Methods

IMPACT and CRASH models

Details of the development of the IMPACT and CRASH prognostic models have been reported.[7,8] In short, the IMPACT models were developed on 8509 patients with moderate or severe TBI (Glasgow Coma Scale [GCS] ≤12) from eight RCTs and three observational studies.[8] The IMPACT models comprise three variants (core, extended, and laboratory) with increasing complexity (Table 1). The models predict mortality and functional outcome at 6 months post-injury.

The two versions of the CRASH prognostic model (basic and computed tomography [CT]; Table 1) were developed on 10,008 TBI patients with GCS ≤14 from one RCT.[7] The models predict mortality at 14 days and functional outcome at 6 months post-injury.

Study design and population

We used data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core study, a prospective, observational cohort study in patients with TBI presenting within 24 h of injury and with an indication for brain CT. Participants were recruited from December 2014 through December 2017 from 59 centers in 18 countries across Europe and Israel. The study protocol of CENTER-TBI has been described.[9] Informed consent by patients and/or legal representative/next of kin were obtained, according to local legislations, for all patients recruited in the CENTER-TBI core dataset and documented in the electronic case report form (e-CRF). Ethical approval was obtained for each recruiting site. The sites, ethical committees, approval numbers, and approval dates are listed on the website: https://www.center-tbi.eu/project/ethical-approval.

Because the IMPACT and CRASH models were developed on different selections of TBI patients, the models were validated on separate cohorts with inclusion criteria corresponding to the development cohorts. For the IMPACT core model, we included patients ≥14 years of age with admission GCS ≤12 and available functional outcome. The validation cohort for the CRASH basic model included patients ≥16 years of age with admission GCS ≤14 and available functional outcome. For validation of the IMPACT and CRASH models that included admission CT and laboratory characteristics, patients without CT scan or blood samples in the first 24 h after injury were excluded. To directly compare performance of the IMPACT and CRASH models, we additionally validated the IMPACT models in the CRASH validation cohort and *vice versa*.

In CENTER-TBI, functional outcome at 6 months post-injury was assessed with the Glasgow Outcome Scale-Extended (GOSE). In line with the original IMPACT and CRASH models, we dichotomized the 6-month GOSE into mortality (GOSE 1) versus survival (GOSE 2–8), and unfavorable (GOSE 1–4) versus favorable (GOSE 5–8) outcome. For the CRASH models, mortality was assessed at 14 days post-injury.

Predictor effects

Definitions and coding of the predictors in the validation cohorts were similar to those in the IMPACT and CRASH development cohorts (Supplementary Tables S1–S3).[7,8] Major extracranial injury was defined as a score of ≥3 on at least one of the extracranial domains of the Abbreviated Injury Scale.[10]

The IMPACT and CRASH logistic regression models were refitted in the validation data to enable comparison of predictor effects between development and validation cohorts. Associations between predictors and outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Validation

The IMPACT and CRASH models were validated by applying the coefficients of the original models to the validation data (Supplementary Tables S2 and S3). Because participating centers in CENTER-TBI were mainly situated in Western countries, we used the CRASH models for high-income countries.[7] Model performance was assessed with discrimination and calibration. Discrimination was expressed with the area under the receiver operating characteristic curve (AUC). The AUC ranges from 0.5 for a non-discriminative model to 1.0 for a perfect model.[11] Calibration indicates the agreement between predicted and observed outcome probabilities. It was assessed graphically by plotting observed frequencies of mortality and unfavorable outcome versus predicted risk. Additionally, we calculated the calibration slope and calibration-in-the-large. The calibration slope is ideally equal to 1 and represents the overall predictor effects in the validation cohort versus the development cohort. Calibration-in-the-large indicates whether predictions are systematically too high or too low, and should ideally be zero.[12]

Model discrimination at external validation may be affected by the distribution of patient characteristics (case mix) in the validation cohort.[13,14] Distinguishing patients with good versus

Table 1. Variables Included in the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation after Significant Head Injury (CRASH) Prognostic Models

IMPACT core	*IMPACT extended*	*IMPACT laboratory*	*CRASH basic*	*CRASH CT*
Age	Core model predictors +	Extended model predictors +	Age	Basic model predictors +
GCS motor score	Hypoxia	Glucose	GCS total score	Petechial hemorrhages
Pupillary reactivity	Hypotension	Hemoglobin	Pupillary reactivity	Obliteration of third ventricle or basal cisterns
	Marshall CT classification		Major extracranial injury	tSAH
	tSAH			Midline shift >5 mm
	EDH			Non-evacuated hematoma

GCS, Glasgow Coma Scale; CT, computed tomography; tSAH, traumatic subarachnoid hemorrhage; EDH, epidural hematoma.

poor outcome is more difficult in a homogeneous cohort than in a heterogeneous population, leading to higher AUCs in heterogeneous cohorts. We therefore calculated the case-mix–corrected AUC, which reflects model discrimination under the assumption that the regression coefficients are correct for the validation population.[14]

Statistical analysis

Statistical analyses were performed with R software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). Calibration plots were created with an updated version of the *val.prob* function (*rms* library in R).[15] Missing 6-month GOSE as a consequence of loss to follow-up (in patients with at least one GOSE observation at another time point) were imputed with a Bayesian mixed-effect model (Supplementary Table S3). Patients without any GOSE observation were excluded from the analyses. Derived variables for GCS (motor) score and pupillary reactivity were generated based on methodology as used in the IMPACT database (Supplementary Table S3).[16] The remaining missing predictor values were statistically imputed with multiple imputation based on the predictors and outcomes included in the IMPACT and CRASH models (*mice* package in R). CENTER-TBI data were collected through the Quesgen e-CRF (Quesgen Systems Inc, Burlingame, CA), hosted on the International Neuroinformatics Coordinating Facility (INCF) platform and extracted by the INCF Neurobot tool (INCF, Sweden). Version Core 1.1 of the CENTER-TBI dataset was used in this study.

Results

Study population

In total, 4509 patients included in the CENTER-TBI core study could be analyzed. Of those, 1173 and 1742 patients met the inclusion criteria for the IMPACT and CRASH validation cohort, respectively (Supplementary Fig. S1). Missing predictor values for the IMPACT (5%) and CRASH (4%) cohorts were imputed (Supplementary Table S4).

The IMPACT validation cohort consisted mainly of severe TBI patients (72%). At 6 months, 347 patients had died (30%), and 644 patients (55%) had unfavorable outcomes (Table 2). In the CRASH validation cohort, one third of the patients had an admission GCS of 13–14. At 14 days, 266 patients had died (15%), and at 6 months, 751 patients (43%) had unfavorable outcomes (Table 2).

Compared to the IMPACT and CRASH development cohorts, patients in the CENTER-TBI validation cohorts were, on average, 20 years older and had more-severe TBI (Table 2). More patients had major extracranial injury in the CRASH validation cohort (49%) than the development cohort (22%). Traumatic subarachnoid hemorrhage occurred almost twice as often in the CENTER-TBI validation cohorts versus the IMPACT and CRASH development cohorts. Overall, functional outcomes at 6 months were poorer in CENTER-TBI, with a higher proportion of unfavorable outcomes in both validation cohorts compared to the development cohorts (Table 2).

IMPACT models

In CENTER-TBI, associations of the predictors in the IMPACT models with 6-month outcome were similar to those reported for the IMPACT development cohort (Supplementary Table S5). However, presence of hypoxia and traumatic subarachnoid hemorrhage did not significantly increase risk of poor outcome in the CENTER-TBI cohort. The IMPACT models distinguished well between patients who died and patients who were alive, indicated by AUCs >0.80 (Table 3). Addition of CT variables to the core model for mortality increased discriminative ability (AUC 0.81 for the core model vs. 0.85 for the extended model; Table 3).

The IMPACT laboratory model for mortality also had an AUC of 0.85 (Table 3). The IMPACT models had slightly lower discriminative ability for unfavorable outcome (AUC core, 0.77; extended, 0.80; laboratory, 0.81; Table 3).

Calibration showed that observed mortality risk was lower than predicted (Supplementary Table S6; Fig. 1) and the IMPACT models slightly over- (core and extended) or underestimated (laboratory) risks for unfavorable outcome (Supplementary Table S6; Fig. 1). Calibration slopes ranged between 1.20 and 1.32 for the models for mortality and between 0.97 and 1.02 for the models for unfavorable outcome (Supplementary Table S6; Fig. 1), reflecting stronger (mortality) or similar (unfavorable outcome) predictor effects in CENTER-TBI versus the IMPACT development cohort.

We observed higher AUCs for the IMPACT models for mortality in the validation cohort compared to the development cohort (e.g., for the laboratory model: AUC 0.85 vs. 0.79, respectively; Table 3). When calculating the case-mix–corrected AUC, these differences in discriminative ability disappeared (Table 3). For the models for unfavorable outcome, the AUC at external validation and the case-mix–corrected AUC were similar, indicating comparable case mix.

CRASH models

Associations between some predictors and outcomes varied between the CENTER-TBI validation cohort versus the CRASH development cohort. For instance, presence of major extracranial injury did not significantly increase mortality risk in CENTER-TBI, and the effect of midline shift was non-significant (Supplementary Table S7).

Discriminative ability of the CRASH models was good for both mortality and unfavorable outcome (Table 3). We observed comparable AUCs for the CT model (0.88 for mortality and 0.84 for unfavorable outcome; Table 3) versus the basic model (0.86 for mortality and 0.82 for unfavorable outcome; Table 3).

Assessment of model calibration revealed differences between observed and predicted risk of mortality and unfavorable outcome for the CRASH CT model (Supplementary Table S6; Fig. 2). The CRASH basic model adequately predicted mortality and unfavorable outcome, whereas the CT model strongly overestimated risk of mortality and unfavorable outcome (Supplementary Table S6; Fig. 2). The moderate calibration slopes for the CRASH CT model reflect the smaller predictor effects in CENTER-TBI compared to the CRASH development cohort (Supplementary Table S6; Fig. 2).

Discriminative ability was similar in the validation versus development cohort, although the validation cohort had a somewhat more homogeneous case mix (Table 3).

Comparison IMPACT and CRASH

When validating the IMPACT models in the broader CRASH selection in CENTER-TBI ($n = 1742$), performance of the IMPACT and CRASH models for mortality and unfavorable outcome was similar (Supplementary Table S8; Supplementary Fig. S2).

Validation of the CRASH models in the stricter IMPACT selection within CENTER-TBI ($n = 1173$) yielded lower AUCs and larger discrepancies between observed and predicted rates of mortality and unfavorable outcome for the CRASH models compared to the IMPACT models (Supplementary Table S8; Supplementary Fig. S3).

Table 2. Characteristics of Patients in the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation after Significant Head Injury (CRASH) Development Cohorts and the IMPACT and CRASH Validation Cohorts in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Core Study

Admission characteristics	*Measure or category*	*IMPACT development cohort* (n = *8509*)	*CENTER-TBI IMPACT validation cohort* (n = *1173*)	*CRASH development cohort* (n = *10,008*)	*CENTER-TBI CRASH validation cohort* (n = *1742*)
Age, years	Median (IQR)	30 (21–45)	49 (29–66)	33 (23–47)	51 (32–67)
GCS motor score	None (1)	1395 (16%)	527 (45%)	—	—
	Extension (2)	1042 (12%)	66 (6%)	—	—
	Abnormal flexion (3)	1085 (13%)	67 (6%)	—	—
	Normal flexion (4)	1940 (23%)	118 (10%)	—	—
	Localizes/obeys (5/6)	2591 (30%)	395 (34%)	—	—
	Untestable/missing (9)	456 (5%)	0 (0%)	—	—
GCS total score (3–14)	Mild (13–14)	—	—	3019 (30%)	582 (33%)
	Moderate (9–12)	—	324 (28%)	3041 (30%)	316 (18%)
	Severe (3–8)	—	849 (72%)	3948 (40%)	844 (48%)
Pupillary reactivity	Both pupils reacted	4486 (53%)	817 (71%)	8057 (81%)	1338 (77)
	One pupil reacted	886 (10%)	99 (8%)	588 (6%)	111 (6%)
	No pupil reacted	1754 (21%)	216 (18%)	825 (8%)	228 (13%)
Major extracranial injury	Yes	—	—	2216 (22%)	845 (49%)
Hypoxia	Yes or suspected	1116 (13%)	198 (17%)	—	—
Hypotension	Yes or suspected	1171 (14%)	187 (16%)	—	—
Marshall CT classification	I	360 (4%)	66 (6%)	—	—
	II	1838 (22%)	413 (35%)	—	—
	III/IV	1050 (12%)	124 (11%)	—	—
	V/VI	1944 (23%)	377 (32%)	—	—
Traumatic subarachnoid hemorrhage	Yes	3313 (39%)	764 (65%)	2458 (25%)	1009 (58%)
Epidural hematoma	Yes	999 (12%)	170 (14%)	—	—
≥1 petechial hemorrhages	Yes	—	—	2238 (22%)	215 (12%)
Obliteration of third ventricle or basal cisterns	Yes	—	—	1827 (18%)	474 (27%)
Midline shift >5 mm	Yes	—	—	1136 (11%)	347 (20%)
Non-evacuated hematoma	Yes	—	—	2111 (21%)	480 (28%)
Glucose (mmol/l)	Median (IQR)	8.2 (6.7–10.4)	7.8 (6.5–9.6)	—	—
Hemoglobin (g/dL)	Median (IQR)	12.7 (10.8–14.3)	13.0 (11.3–14.2)	—	—
Mortality at 14 days	Yes	—	—	1948 (19%)	266 (15%)
Outcome at 6 months	Dead	2396 (28%)	347 (30%)	2323 (23%)	394 (23%)
	Vegetative[a]	351 (4%)	0 (0%)	272 (3%)	0 (0%)
	Lower severe disability	—	243 (21%)	—	291 (17%)
	Upper severe disability	1335 (16%)	54 (5%)	962 (10%)	66 (4%)
	Lower moderate disability	—	91 (8%)	—	138 (8%)
	Upper moderate disability	1666 (20%)	148 (13%)	1664 (17%)	212 (12%)
	Lower good recovery	—	147 (13%)	—	267 (15%)
	Upper good recovery	2761 (32%)	143 (12%)	4333 (43%)	374 (22%)
	Death or severe disability	4082 (48%)	644 (55%)	3557 (36%)	751 (43%)

[a]Vegetative state and lower severe disability combined (GOSE categories 2 and 3). IMPACT, International Mission on Prognosis and Analysis of Clinical Trials; CRASH, Corticoid Randomisation After Significant Head injury; CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; IQR, interquartile range; GCS, Glasgow Coma Scale; CT, computed tomography.

Discussion

We performed detailed evaluations of the external validity of the IMPACT and CRASH prognostic models in a large contemporary European cohort of TBI patients. Both sets of models showed good discriminative ability, which modestly improved with addition of CT variables to the IMPACT core and CRASH basic models. There were substantial differences between observed and predicted outcome risk, specifically for the CRASH CT model.

Over the past decade, the IMPACT and CRASH models have been externally validated in many different, but mostly small, selected or single-country cohorts. A recent systematic review on prognostic models in moderate and severe TBI showed that discriminative ability of the IMPACT and CRASH models at external validation was moderate to good across different settings (mean AUCs weighted for sample size, 0.77–0.82 over 91 validations).[4] Calibration was, however, highly variable and substantial miscalibration was observed in subgroups of TBI patients (e.g., patients who underwent decompressive craniectomy). Compared to previous external validation studies, the IMPACT and CRASH models performed generally well in the CENTER-TBI validation cohort, indicating that the models stood the test of time.[4] Overall,

Table 3. Discriminative Ability of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation after Significant Head Injury (CRASH) Models in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Core Study

Mortality *Performance measure*	*IMPACT core* (n = *1173*)	*IMPACT extended* (n = *1030*)	*IMPACT laboratory* (n = *1006*)	*CRASH basic* (n = *1742*)	*CRASH CT* (n = *1542*)
AUC, development (internal validation)	0.77	0.81	0.79	0.86	0.88
AUC, external validation	0.81 (0.79–0.84)	0.85 (0.82–0.87)	0.85 (0.82–0.87)	0.86 (0.83–0.88)	0.88 (0.86–0.90)
AUC, case-mix corrected	0.77 (0.75–0.80)	0.80 (0.76–0.82)	0.79 (0.77–0.83)	0.86 (0.84–0.88)	0.91 (0.87–0.91)
Unfavorable outcome *Performance measure*	*IMPACT core* (n = *1173*)	*IMPACT extended* (n = *1030*)	*IMPACT laboratory* (n = *1006*)	*CRASH basic* (n = *1742*)	*CRASH CT* (n = *1542*)
AUC, development (internal validation)	0.78	0.81	0.81	0.81	0.83
AUC, external validation	0.77 (0.74–0.80)	0.80 (0.78–0.83)	0.81 (0.78–0.84)	0.82 (0.80–0.84)	0.84 (0.82–0.86)
AUC, case-mix corrected	0.78 (0.74–0.79)	0.80 (0.79–0.84)	0.81 (0.78–0.84)	0.83 (0.81–0.85)	0.86 (0.84–0.88)

All performance values for external validation are reported with a 95% confidence interval. IMPACT, International Mission on Prognosis and Analysis of Clinical Trials; CRASH, Corticoid Randomisation After Significant Head injury; CT, computed tomography; AUC, area under the receiver operating characteristic curve.

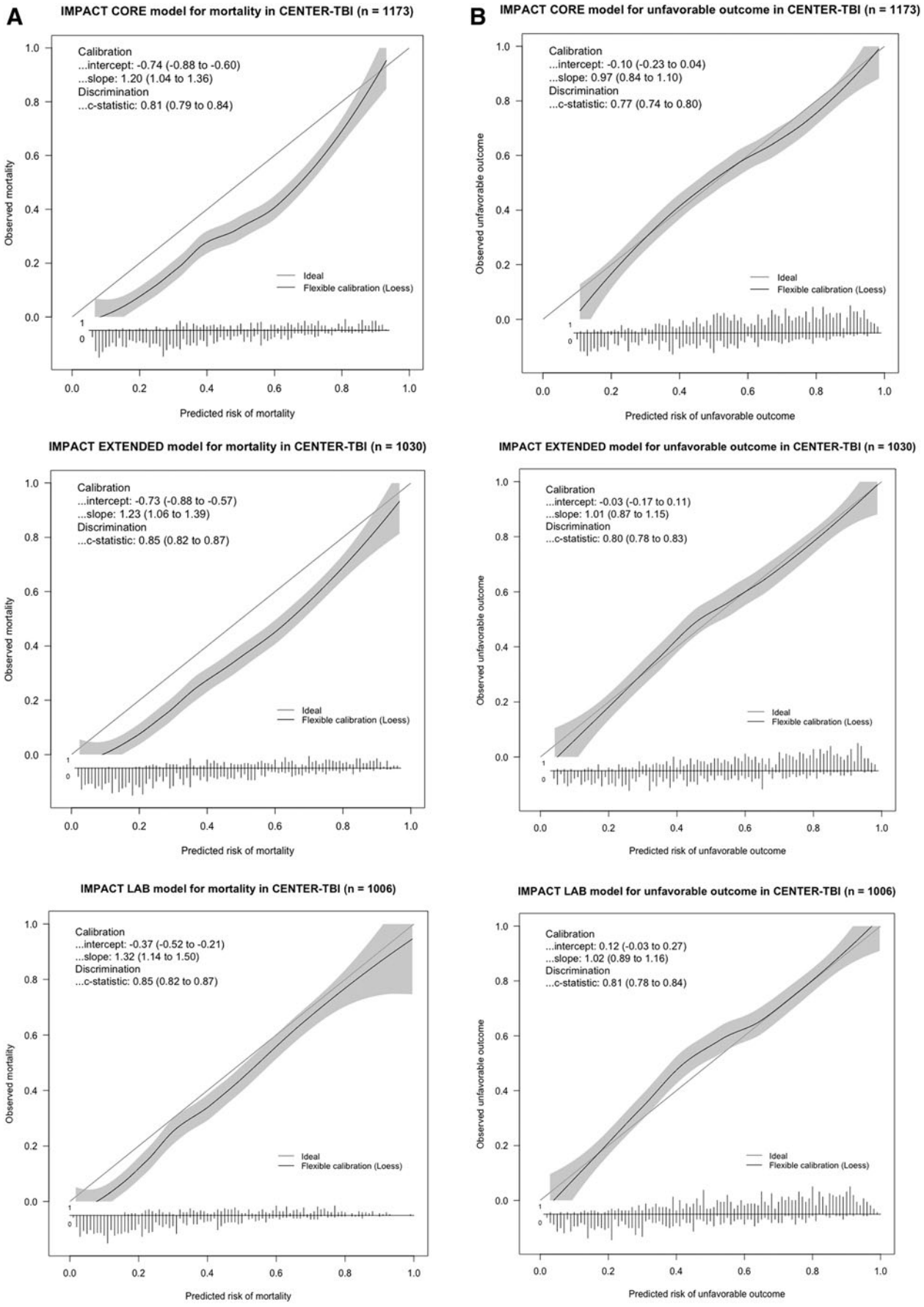
observed mortality was lower than predicted, and observed unfavorable outcome was similar as predicted, which may indicate that survival has improved over time, but more patients survive with (severe) disabilities.

Our validation cohort was part of a large and unique multi-center observational study with data from contemporary TBI patients throughout Europe.[9] We could validate the original IMPACT and CRASH models because of availability of all included predictors and outcomes. However, discrepancies might still exist in the assessment method and definitions of predictors and outcomes. For example, imaging techniques may have improved or changed over time.[13] Another limitation of our study is that the CRASH models for low- to middle-income countries could not be validated because mainly high-income countries participated in CENTER-TBI.

Model performance at external validation is sensitive to several study characteristics.[13] Differences in case mix in the validation cohorts compared to the development cohorts influenced the discriminative ability of the IMPACT and CRASH models. The CENTER-TBI validation cohort generally consisted of older and more severely affected TBI patients and was more heterogeneous than the IMPACT database, which predominantly included RCTs.[8,16] The CENTER-TBI cohort was somewhat more homogeneous than the CRASH trial, which fits with the relatively broad inclusion criteria in that trial.[17] We observed substantial miscalibration for the IMPACT and CRASH models in CENTER-TBI. This could be explained by differences in prevalence and effects of predictors between the derivation and validation cohorts. Major extracranial injury, traumatic subarachnoid hemorrhage, and midline shift were more prevalent in CENTER-TBI than in the CRASH development cohort, whereas mortality at 14 days was similar (Table 2). Presence of midline shift was not associated with mortality and unfavorable outcome in CENTER-TBI (Supplementary Table S7). This may explain the substantial overestimation of mortality and unfavorable outcome by the CRASH CT model.[14]

Overall, discriminative ability of the IMPACT and CRASH models only marginally improved with increasing model complexity. This observation confirms that the core clinical predictors (age, GCS [motor], score, and pupillary reactivity) are essential for adequate identification of TBI patients at high risk of mortality or unfavorable outcome, and that additional predictors add relatively little prognostic information. Calibration of the IMPACT core models was similar or inferior compared to the more-complex models (Supplementary Table S6; Fig. 1). This underscores the need for model updating (e.g., refitting the model intercept or refitting the coefficients) to adjust models to specific clinical settings.[11,18] Extension of the IMPACT and CRASH models with new predictors has been attempted previously, but did not yield substantial improvement in model performance.[4] In CENTER-TBI, updating the IMPACT (and CRASH) models may be pursued.[19,20] For instance, performance of the IMPACT extended model may be improved by replacing the Marshall CT classification with a more-recent CT score (e.g., Rotterdam or Helsinki) or a combination of

FIG. 1. Calibration plots of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) models for (**A**) mortality and (**B**) unfavorable outcome at 6 months. Predicted probabilities are on the x-axis and observed outcomes on the y-axis. The distribution of the predicted probabilities is shown at the bottom of the graphs, separate for those with (=1) and without (=0) the outcome of interest. The 45-degree line with intercept 0 and slope 1 represents perfect agreement between predicted and observed outcome rates. Deviation above or below this line indicates that the model under- or overestimates mortality or unfavorable outcome rates, respectively. For instance, the calibration plots in (A) show that all three IMPACT models tend to overestimate mortality rates in the CENTER-TBI validation cohort. CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury.



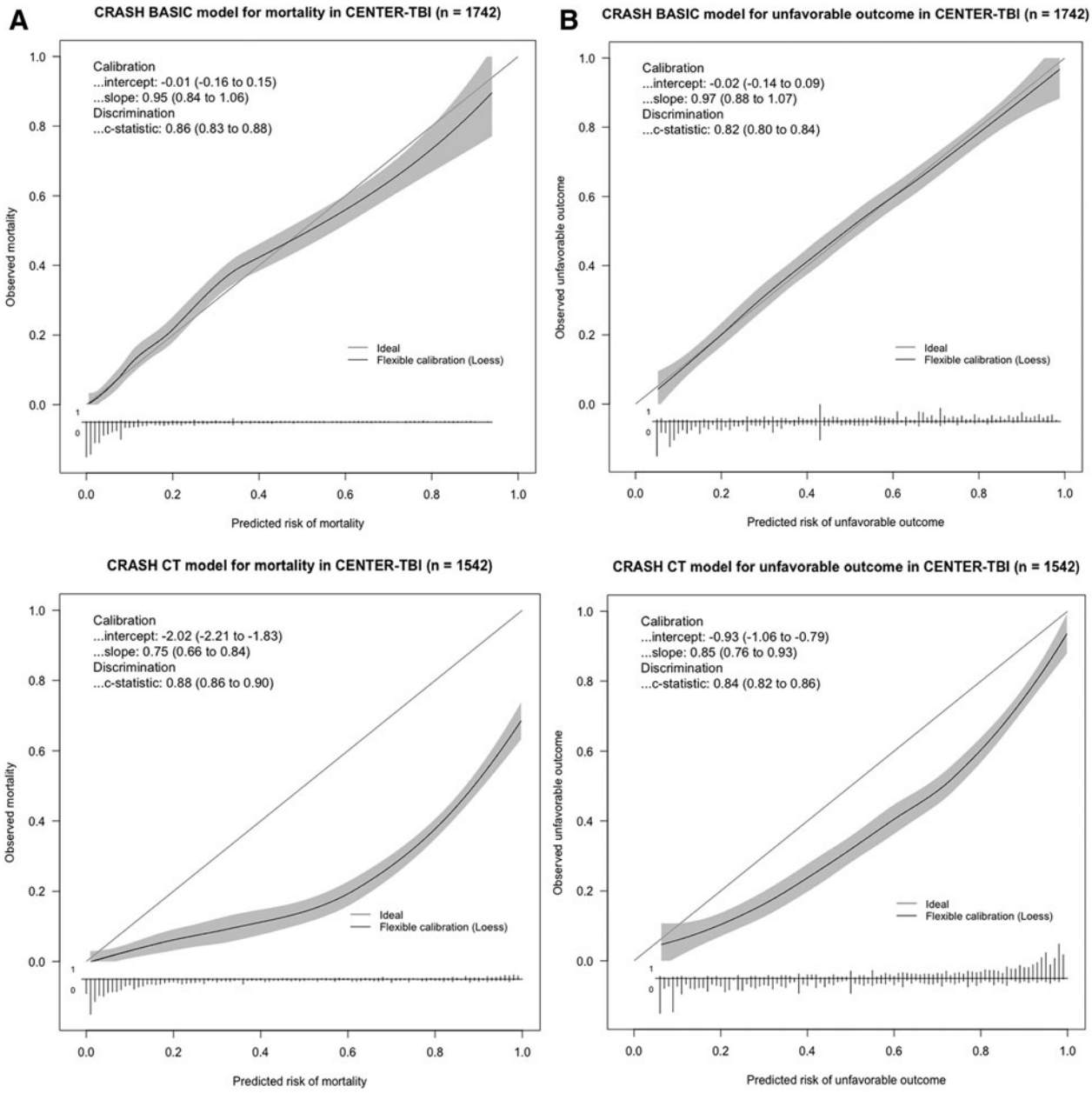


FIG. 2. Calibration plots of the Corticoid Randomisation After Significant Head injury (CRASH) models for (**A**) mortality at 14 days and (**B**) unfavorable outcome at 6 months. Predicted probabilities are on the x-axis and observed outcomes on the y-axis. The distribution of the predicted probabilities is shown at the bottom of the graphs, separate for those with (=1) and without (=0) the outcome of interest. The 45-degree line with intercept 0 and slope 1 represents perfect agreement between predicted and observed outcome rates. Deviation above or below this line indicates that the model under- or overestimates mortality or unfavorable outcome rates, respectively. For instance, the CRASH CT model overestimates mortality and unfavorable outcome rates in the CENTER-TBI validation cohort. CT, computed tomography; CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury.

individual CT characteristics.[21,22] Also, the models could be enriched with promising biomarkers or dynamic characteristics obtained during the clinical course.[23]

Continuous external validation of prognostic models for moderate and severe TBI in recent cohorts has been recommended.[4,23,24] The IMPACT and CRASH models were developed on relatively historic data, whereas the epidemiology of TBI has changed substantially over the last years (e.g., regarding age distribution).[1] This study adds to the existing evidence by showing that the IMPACT and CRASH models are valid for outcome prediction in contemporary TBI patients across Europe. Nevertheless, discrepancies between observed and predicted rates of mortality and unfavorable outcome exist for both sets of models. Adjustment of the models to local hospital and patient characteristics is therefore strongly recommended.

Performance of the IMPACT and CRASH models in the broadest selection of TBI patients was comparable. The additional effect of major extracranial injury in CRASH seems limited,

probably because patients in CENTER-TBI were selected based on TBI and not any trauma.[10] The decision on which model to use should mainly be guided by the characteristics of a specific setting or population (e.g., TBI severity, country economic status). Use of either the IMPACT or CRASH model and degree of complexity of the model also depends on availability of predictors. Given that the substantial uncertainty on likely outcomes in individual patients, the IMPACT and CRASH models are not recommended for clinical decision making. Treatment options for TBI patients are scarce, and documenting prognosis in the intensive care setting does not seem to substantially affect treatment decisions.[25–27]

On the other hand, there is an increasing recognition that estimates of prognosis by clinicians are often unduly pessimistic for TBI patients,[28] and regular comparison of outcome predicted by these models with clinical expectations may help individual clinicians calibrate their prognostication and practice. Based on the good discriminative ability of the IMPACT and CRASH models, potential applications in research settings are risk stratification in trials and covariate adjustment in statistical analyses to increase statistical power. The models may also provide a point of reference for quality of care by comparing observed versus expected outcomes.[3]

Conclusions

The IMPACT and CRASH models adequately identify patients at high risk for mortality or unfavorable outcome, which supports their use in research settings and for benchmarking in the context of quality-of-care assessment.

Acknowledgments

We are grateful to all patients that participated in the CENTER-TBI study to help us in our efforts to improve care and outcome for TBI.

The CENTER-TBI Participants and Investigators

Cecilia Åkerlund,[1] Krisztina Amrein,[2] Nada Andelic,[3] Lasse Andreassen,[4] Audny Anke,[5] Anna Antoni,[6] Gérard Audibert,[7] Philippe Azouvi,[8] Maria Luisa Azzolini,[9] Ronald Bartels,[10] Pál Barzó,[11] Romuald Beauvais,[12] Ronny Beer,[13] Bo-Michael Bellander,[14] Antonio Belli,[15] Habib Benali,[16] Maurizio Berardino,[17] Luigi Beretta,[9] Morten Blaabjerg,[18] Peter Bragge,[19] Alexandra Brazinova,[20] Vibeke Brinck,[21] Joanne Brooker,[22] Camilla Brorsson,[23] Andras Buki,[24] Monika Bullinger,[25] Manuel Cabeleira,[26] Alessio Caccioppola,[27] Emiliana Calappi,[27] Maria Rosa Calvi,[9] Peter Cameron,[28] Guillermo Carbayo Lozano,[29] Marco Carbonara,[27] Giorgio Chevallard,[30] Arturo Chieregato,[30] Giuseppe Citerio,[31,32] Maryse Cnossen,[33] Mark Coburn,[34] Jonathan Coles,[35] Jamie D. Cooper,[36] Marta Correia,[37] Amra Čović,[38] Nicola Curry,[39] Endre Czeiter,[24] Marek Czosnyka,[26] Claire Dahyot Fizelier,[40] Helen Dawes,[41] Véronique De Keyser,[42] Vincent Degos,[16] Francesco Della Corte,[43] Hugo den Boogert,[10] Bart Depreitere,[44] Đula Đilvesi,[45] Abhishek Dixit,[46] Emma Donoghue,[22] Jens Dreier,[47] Guy Loup Dulière,[48] Ari Ercole,[46] Patrick Esser,[41] Erzsébet Ezer,[49] Martin Fabricius,[50] Valery L. Feigin,[51] Kelly Foks,[52] Shirin Frisvold,[53] Alex Furmanov,[54] Pablo Gagliardo,[55] Damien Galanaud,[16] Dashiell Gantner,[28] Guoyi Gao,[56] Pradeep George,[57] Alexandre Ghuysen,[58] Lelde Giga,[59] Ben Glocker,[60] Jagoš Golubovic,[45] Pedro A. Gomez,[61] Johannes Gratz,[62] Benjamin Gravesteijn,[33] Francesca Grossi,[43] Russell L. Gruen,[63] Deepak Gupta,[64] Juanita A. Haagsma,[33] Iain Haitsma,[65] Raimund Helbok,[13] Eirik Helseth,[66] Lindsay Horton,[67] Jilske Huijben,[33] Peter J. Hutchinson,[68] Bram Jacobs,[69] Stefan Jankowski,[70] Mike Jarrett,[21] Ji-Yao Jiang,[56] Kelly Jones,[51] Mladen Karan,[47] Angelos G. Kolias,[68] Erwin Kompanje,[71] Daniel Kondziella,[50] Evgenios Koraropoulos,[46] Lars Owe Koskinen,[72] Noémi Kovács,[73] Alfonso Lagares,[61] Linda Lanyon,[57] Steven Laureys,[74] Fiona Lecky,[75] Rolf Lefering,[76] Valerie Legrand,[77] Aurelie Lejeune,[78] Leon Levi,[79] Roger Lightfoot,[80] Hester Lingsma,[33] Andrew I.R. Maas,[42] Ana M. Castaño León,[61] Marc Maegele,[81] Marek Majdan,[20] Alex Manara,[82] Geoffrey Manley,[83] Costanza Martino,[84] Hugues Maréchal,[48] Julia Mattern,[85] Catherine McMahon,[86] Béla Melegh,[87] David Menon,[46] Tomas Menovsky,[42] Davide Mulazzi,[27] Visakh Muraleedharan,[57] Lynnette Murray,[28] Nandesh Nair,[42] Ancuta Negru,[88] David Nelson,[1] Virginia Newcombe,[46] Daan Nieboer,[33] Quentin Noirhomme,[74] József Nyirádi,[2] Otesile Olubukola,[75] Matej Oresic,[89] Fabrizio Ortolano,[27] Aarno Palotie,[90,91,92] Paul M. Parizel,[93] Jean François Payen,[94] Natascha Perera,[12] Vincent Perlbarg,[16] Paolo Persona,[95] Wilco Peul,[96] Anna Piippo-Karjalainen,[97] Matti Pirinen,[90] Horia Ples,[88] Suzanne Polinder,[33] Inigo Pomposo,[29] Jussi P. Posti,[98] Louis Puybasset,[99] Andreea Radoi,[100] Arminas Ragauskas,[101] Rahul Raj,[97] Malinka Rambadagalla,[102] Ruben Real,[38] Jonathan Rhodes,[103] Sylvia Richardson,[104] Sophie Richter,[46] Samuli Ripatti,[90] Saulius Rocka,[101] Cecilie Roe,[105] Olav Roise,[106] Jonathan Rosand,[107] Jeffrey V. Rosenfeld,[108] Christina Rosenlund,[109] Guy Rosenthal,[54] Rolf Rossaint,[34] Sandra Rossi,[95] Daniel Rueckert,[60] Martin Rusnák,[110] Juan Sahuquillo,[100] Oliver Sakowitz,[85,111] Renan Sanchez Porras,[111] Janos Sandor,[112] Nadine Schäfer,[76] Silke Schmidt,[113] Herbert Schoechl,[114] Guus Schoonman,[115] Rico Frederik Schou,[116] Elisabeth Schwendenwein,[6] Charlie Sewalt,[33] Toril Skandsen,[117,118] Peter Smielewski,[26] Abayomi Sorinola,[119] Emmanuel Stamatakis,[46] Simon Stanworth,[39] Ana Stevanovic,[34] Robert Stevens,[120] William Stewart,[121] Ewout W. Steyerberg,[33,122] Nino Stocchetti,[123] Nina Sundström,[124] Anneliese Synnot,[22,125] Riikka Takala,[126] Viktória Tamás,[119] Tomas Tamosuitis,[127] Mark Steven Taylor,[20] Braden Te Ao,[51] Olli Tenovuo,[98] Alice Theadom,[51] Matt Thomas,[82] Dick Tibboel,[128] Marjolein Timmers,[71] Christos Tolias,[129] Tony Trapani,[28] Cristina Maria Tudora,[88] Peter Vajkoczy,[130] Shirley Vallance,[28] Egils Valeinis,[59] Zoltán Vámos,[49] Gregory Van der Steen,[42] Joukje van der Naalt,[69] Jeroen T.J.M. van Dijck,[96] Thomas A. van Essen,[96] Wim Van Hecke,[131] Caroline van Heugten,[132] Dominique Van Praag,[133] Thijs Vande Vyvere,[131] Audrey Vanhaudenhuyse,[16,74] Roel P.J. van Wijk,[97] Alessia Vargiolu,[32] Emmanuel Vega,[79] Kimberley Velt,[33] Jan Verheyden,[131] Paul M. Vespa,[134] Anne Vik,[117,135] Rimantas Vilcinis,[127] Victor Volovici,[65] Nicole von Steinbüchel,[38] Daphne Voormolen,[33] Petar Vulekovic,[45] Kevin K.W. Wang,[136] Eveline Wiegers,[33] Guy Williams,[46] Lindsay Wilson,[67] Stefan Winzeck,[46] Stefan Wolf,[137] Zhihui Yang,[136] Peter Ylén,[138] Alexander Younsi,[85] Frederik A. Zeiler,[46,139] Veronika Zelinkova,[20] Agate Ziverte,[59] and Tommaso Zoerle[27]

[1]Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden

[2]János Szentágothai Research Centre, University of Pécs, Pécs, Hungary

[3]Division of Surgery and Clinical Neuroscience, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway

[4]Department of Neurosurgery, University Hospital Northern Norway, Tromso, Norway

[5]Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromso, Norway

[6]Trauma Surgery, Medical University Vienna, Vienna, Austria

[7]Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France

[8]Raymond Poincare Hospital, Assistance Publique–Hopitaux de Paris, Paris, France
[9]Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy
[10]Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The Netherlands
[11]Department of Neurosurgery, University of Szeged, Szeged, Hungary
[12]International Projects Management, ARTTIC, Munchen, Germany
[13]Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria
[14]Department of Neurosurgery & Anesthesia & Intensive Care Medicine, Karolinska University Hospital, Stockholm, Sweden
[15]NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, United Kingdom
[16]Anesthesie-Réanimation, Assistance Publique–Hopitaux de Paris, Paris, France
[17]Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino–Orthopedic and Trauma Center, Torino, Italy
[18]Department of Neurology, Odense University Hospital, Odense, Denmark
[19]BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Clayton, Victoria, Australia
[20]Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia
[21]Quesgen Systems Inc., Burlingame, California, USA
[22]Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[23]Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden
[24]Department of Neurosurgery, Medical School, University of Pécs, Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Pécs, Hungary
[25]Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
[26]Brain Physics Lab, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom
[27]Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
[28]ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia
[29]Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain
[30]NeuroIntensive Care, Niguarda Hospital, Milan, Italy
[31]School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy
[32]NeuroIntensive Care, ASST di Monza, Monza, Italy
[33]Department of Public Health, Erasmus Medical Center–University Medical Center, Rotterdam, The Netherlands
[34]Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany
[35]Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, United Kingdom
[36]School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia
[37]Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, United Kingdom
[38]Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany
[39]Oxford University Hospitals NHS Trust, Oxford, United Kingdom
[40]Intensive Care Unit, CHU Poitiers, Potiers, France
[41]Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, United Kingdom
[42]Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
[43]Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy
[44]Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium
[45]Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[46]Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom
[47]Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[48]Intensive Care Unit, CHR Citadelle, Liège, Belgium
[49]Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary
[50]Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark
[51]National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand
[52]Department of Neurology, Erasmus MC, Rotterdam, The Netherlands
[53]Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromso, Norway
[54]Department of Neurosurgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[55]Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain
[56]Department of Neurosurgery, Shanghai Renji Hospital, Shanghai Jiaotong University/School of Medicine, Shanghai, China
[57]Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden
[58]Emergency Department, CHU, Liège, Belgium
[59]Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia
[60]Department of Computing, Imperial College London, London, United Kingdom
[61]Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain
[62]Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Vienna, Austria
[63]College of Health and Medicine, Australian National University, Canberra, Australia
[64]Department of Neurosurgery, Neurosciences Centre & JPN Apex Trauma Centre, All India Institute of Medical Sciences, New Delhi, India
[65]Department of Neurosurgery, Erasmus MC, Rotterdam, The Netherlands
[66]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

[67]Division of Psychology, University of Stirling, Stirling, United Kingdom
[68]Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, United Kingdom
[69]Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[70]Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom
[71]Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
[72]Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden
[73]Hungarian Brain Research Program–Grant No. KTIA_13_NAP-A-II/8, University of Pécs, Pécs, Hungary
[74]Cyclotron Research Center, University of Liège, Liège, Belgium
[75]Emergency Medicine Research in Sheffield, Health Services Research Section, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, United Kingdom
[76]Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany
[77]VP Global Project Management CNS, ICON, Paris, France
[78]Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France
[79]Department of Neurosurgery, Rambam Medical Center, Haifa, Israel
[80]Department of Anesthesiology & Intensive Care, University Hospitals Southhampton NHS Trust, Southampton, United Kingdom
[81]Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany
[82]Intensive Care Unit, Southmead Hospital, Bristol, Bristol, United Kingdom
[83]Department of Neurological Surgery, University of California, San Francisco, California, USA
[84]Department of Anesthesia & Intensive Care, M. Bufalini Hospital, Cesena, Italy
[85]Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany
[86]Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom
[87]Department of Medical Genetics, University of Pécs, Pécs, Hungary
[88]Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania
[89]School of Medical Sciences, Örebro University, Örebro, Sweden
[90]Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
[91]Analytic and Translational Genetics Unit, Department of Medicine; Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA
[92]Program in Medical and Population Genetics; The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
[93]Department of Radiology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
[94]Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France
[95]Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy
[96]Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Department of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands
[97]Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland
[98]Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland
[99]Department of Anesthesiology and Critical Care, Pitié-Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France
[100]Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain
[101]Department of Neurosurgery, Kaunas University of Technology and Vilnius University, Vilnius, Lithuania
[102]Department of Neurosurgery, Rezekne Hospital, Rezekne, Latvia
[103]Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburg, Edinburgh, United Kingdom
[104]Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, United Kingdom
[105]Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway
[106]Division of Surgery and Clinical Neuroscience, Oslo University Hospital, Oslo, Norway
[107]Broad Institute, Cambridge MA Harvard Medical School, Boston, Massachusetts, USA and Massachusetts General Hospital, Boston, Massachusetts, USA
[108]National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
[109]Department of Neurosurgery, Odense University Hospital, Odense, Denmark
[110]International Neurotrauma Research Organisation, Vienna, Austria
[111]Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany
[112]Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary
[113]Department Health and Prevention, University Greifswald, Greifswald, Germany
[114]Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria
[115]Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, The Netherlands
[116]Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark
[117]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
[118]Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[119]Department of Neurosurgery, University of Pécs, Pécs, Hungary
[120]Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA
[121]Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK
[122]Dept. of Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

[123]Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
[124]Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden
[125]Cochrane Consumers and Communication Review Group, Centre for Health Communication and Participation, School of Psychology and Public Health, La Trobe University, Melbourne, Victoria, Australia
[126]Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland
[127]Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania
[128]Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
[129]Department of Neurosurgery, Kings College London, London, United Kingdom
[130]Neurologie, Neurochirurgie und Psychiatrie, Charité–Universitätsmedizin Berlin, Berlin, Germany
[131]icoMetrix NV, Leuven, Belgium
[132]Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, United Kingdom
[133]Psychology Department, Antwerp University Hospital, Edegem, Belgium
[134]Director of Neurocritical Care, University of California, Los Angeles, Los Angeles, California, USA
[135]Department of Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[136]Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA
[137]Department of Neurosurgery, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[138]VTT Technical Research Centre, Tampere, Finland
[139]Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

Funding Information

The research leading to these results was supported by the European Union's Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 602150 (CENTER-TBI). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA), and from Integra LifeSciences Corporation (USA).

The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Disclosure Statement

No competing financial interests exist.

References

1. Maas, A.I.R., Menon, D.K., Adelson, P.D., Andelic, N., Bell, M.J., Belli, A., Bragge, P., Brazinova, A., Buki, A., Chesnut, R.M., Citerio, G., Coburn, M., Cooper, D.J., Crowder, A.T., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J.P., Duhaime, A.C., Ercole, A., van Essen, T.A., Feigin, V.L., Gao, G., Giacino, J., Gonzalez-Lara, L.E., Gruen, R.L., Gupta, D., Hartings, J.A., Hill, S., Jiang, J.Y., Ketharanathan, N., Kompanje, E.J.O., Lanyon, L., Laureys, S., Lecky, F., Levin, H., Lingsma, H.F., Maegele, M., Majdan, M., Manley, G., Marsteller, J., Mascia, L., McFadyen, C., Mondello, S., Newcombe, V., Palotie, A., Parizel, P.M., Peul, W., Piercy, J., Polinder, S., Puybasset, L., Rasmussen, T.E., Rossaint, R., Smielewski, P., Soderberg, J., Stanworth, S.J., Stein, M.B., von Steinbuchel, N., Stewart, W., Steyerberg, E.W., Stocchetti, N., Synnot, A., Te Ao, B., Tenovuo, O., Theadom, A., Tibboel, D., Videtta, W., Wang, K.K.W., Williams, W.H., Wilson, L., and Yaffe, K.; InTBIR Participants and Investigators. (2017). Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol. 16, 987–1048.
2. Thompson, D.D., Lingsma, H.F., Whiteley, W.N., Murray, G.D., and Steyerberg, E.W. (2015). Covariate adjustment had similar benefits in small and large randomized controlled trials. J. Clin. Epidemiol. 68, 1068–1075.
3. Huijben, J.A., Wiegers, E.J.A., de Keizer, N.F., Maas, A.I.R., Menon, D., Ercole, A., Citerio, G., Lecky, F., Wilson, L., Cnossen, M.C., Polinder, S., Steyerberg, E.W., van der Jagt, M., Lingsma, H.F., and the Delphi panel. (2019). Development of a quality indicator set to measure and improve quality of ICU care for patients with traumatic brain injury. Crit. Care 23, 95.
4. Dijkland, S.A., Foks, K.A., Polinder, S., Dippel, D.W.J., Maas, A., Lingsma, H., and Steyerberg, E.W. (2020). Prognosis in moderate and severe traumatic brain injury: a systematic review of contemporary models and validation studies. J. Neurotrauma 37, 1–13.
5. Mushkudiani, N.A., Hukkelhoven, C.W., Hernandez, A.V., Murray, G.D., Choi, S.C., Maas, A.I., and Steyerberg, E.W. (2008). A systematic review finds methodological improvements necessary for prognostic models in determining traumatic brain injury outcomes. J. Clin. Epidemiol. 61, 331–343.
6. Perel, P., Edwards, P., Wentz, R., and Roberts, I. (2006). Systematic review of prognostic models in traumatic brain injury. BMC Med. Inform. Decis. Mak. 6, 38.
7. MRC CRASH Trial Collaborators. (2008). Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ 336, 425–429.
8. Steyerberg, E.W., Mushkudiani, N., Perel, P., Butcher, I., Lu, J., McHugh, G.S., Murray, G.D., Marmarou, A., Roberts, I., Habbema, J.D., and Maas, A.I. (2008). Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 5, e165; discussion, e165.
9. Maas, A.I., Menon, D.K., Steyerberg, E.W., Citerio, G., Lecky, F., Manley, G.T., Hill, S., Legrand, V., and Sorgner, A.; CENTER-TBI Participants and Investigators. (2015). Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 76, 67–80.
10. van Leeuwen, N., Lingsma, H.F., Perel, P., Lecky, F., Roozenbeek, B., Lu, J., Shakur, H., Weir, J., Steyerberg, E.W., and Maas, A.I.; International Mission on Prognosis and Clinical Trial Design in TBI Study Group; Corticosteroid Randomization After Significant Head Injury Trial Collaborators; Trauma Audit and Research Network. (2012). Prognostic value of major extracranial injury in traumatic brain injury: an individual patient data meta-analysis in 39,274 patients. Neurosurgery 70, 811–818; discussion, 818.
11. Steyerberg, E.W. (2009). Validation of prediction models, in: *Clinical Prediction Models: A Practical Approach to Development, Validation and Updating*. Springer: New York, pps. 299–310.
12. Steyerberg, E.W., Vickers, A.J., Cook, N.R., Gerds, T., Gonen, M., Obuchowski, N., Pencina, M.J., and Kattan, M.W. (2010). Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 21, 128–138.
13. Damen, J., Debray, T.P.A., Pajouheshnia, R., Reitsma, J.B., Scholten, R., Moons, K.G.M., and Hooft, L. (2019). Empirical evidence of the impact of study characteristics on the performance of prediction models: a meta-epidemiological study. BMJ Open 9, e026160.
14. Vergouwe, Y., Moons, K.G., and Steyerberg, E.W. (2010). External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. Am. J. Epidemiol. 172, 971–980.
15. Van Calster, B., Nieboer, D., Vergouwe, Y., De Cock, B., Pencina, M.J., and Steyerberg, E.W. (2016). A calibration hierarchy for risk models was defined: from utopia to empirical data. J. Clin. Epidemiol. 74, 167–176.

16. Marmarou, A., Lu, J., Butcher, I., McHugh, G.S., Mushkudiani, N.A., Murray, G.D., Steyerberg, E.W., and Maas, A.I. (2007). IMPACT database of traumatic brain injury: design and description. J. Neurotrauma 24, 239–250.
17. Roberts, I., Yates, D., Sandercock, P., Farrell, B., Wasserberg, J., Lomas, G., Cottingham, R., Svoboda, P., Brayley, N., Mazairac, G., Laloe, V., Munoz-Sanchez, A., Arango, M., Hartzenberg, B., Khamis, H., Yutthakasemsunt, S., Komolafe, E., Olldashi, F., Yadav, Y., Murillo-Cabezas, F., Shakur, H., and Edwards, P.; CRASH trial collaborators. (2004). Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 364, 1321–1328.
18. Vergouwe, Y., Nieboer, D., Oostenbrink, R., Debray, T.P.A., Murray, G.D., Kattan, M.W., Koffijberg, H., Moons, K.G.M., and Steyerberg, E.W. (2017). A closed testing procedure to select an appropriate method for updating prediction models. Stat. Med. 36, 4529–4539.
19. Nieboer, D., Vergouwe, Y., Ankerst, D.P., Roobol, M.J., and Steyerberg, E.W. (2016). Improving prediction models with new markers: a comparison of updating strategies. BMC Med. Res. Methodol. 16, 128.
20. Siregar, S., Nieboer, D., Versteegh, M.I.M., Steyerberg, E.W., and Takkenberg, J.J.M. (2019). Methods for updating a risk prediction model for cardiac surgery: a statistical primer. Interact. Cardiovasc. Thorac. Surg. 28, 333–338.
21. Maas, A.I., Hukkelhoven, C.W., Marshall, L.F., and Steyerberg, E.W. (2005). Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery 57, 1173–1182; discussion, 1173–1182.
22. Thelin, E.P., Nelson, D.W., Vehvilainen, J., Nystrom, H., Kivisaari, R., Siironen, J., Svensson, M., Skrifvars, M.B., Bellander, B.M., and Raj, R. (2017). Evaluation of novel computerized tomography scoring systems in human traumatic brain injury: an observational, multicenter study. PLoS Med 14, e1002368.
23. Lingsma, H.F., Roozenbeek, B., Steyerberg, E.W., Murray, G.D., and Maas, A.I. (2010). Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol. 9, 543–554.
24. Roozenbeek, B., Lingsma, H.F., Lecky, F.E., Lu, J., Weir, J., Butcher, I., McHugh, G.S., Murray, G.D., Perel, P., Maas, A.I., and Steyerberg, E.W.; International Mission on Prognosis Analysis of Clinical Trials in Traumatic Brain Injury Study Group: Corticosteroid Randomisation After Significant Head Injury (CRASH) Trial Collaborators; Trauma Audit and Research Network (TARN). (2012). Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models. Crit. Care Med. 40, 1609–1617.
25. Carter, E.L., Hutchinson, P.J., Kolias, A.G., and Menon, D.K. (2016). Predicting the outcome for individual patients with traumatic brain injury: a case-based review. Br. J. Neurosurg. 30, 227–232.
26. Letsinger, J., Rommel, C., Hirschi, R., Nirula, R., and Hawryluk, G.W.J. (2017). The aggressiveness of neurotrauma practitioners and the influence of the IMPACT prognostic calculator. PLoS One 12, e0183552.
27. Turnbull, A.E., Hayes, M.M., Brower, R.G., Colantuoni, E., Basyal, P.S., White, D.B., Curtis, J.R., and Needham, D.M. (2019). Effect of documenting prognosis on the information provided to ICU proxies: a randomized trial. Crit. Care Med. 47, 757–764.
28. Harvey, D., Butler, J., Groves, J., Manara, A., Menon, D., Thomas, E., and Wilson, M. (2018). Management of perceived devastating brain injury after hospital admission: a consensus statement from stakeholder professional organizations. Br. J. Anaesth. 120, 138–145.

Address correspondence to:
Simone A. Dijkland, MD, PhD
Department of Public Health
Center for Medical Decision Making
Erasmus MC-University Medical Center
PO Box 2040
3000 CA Rotterdam
The Netherlands

E-mail: s.dijkland@erasmusmc.nl