Prognosis in moderate and severe traumatic brain injury: External validation of the IMPACT models and the role of extracranial injuries

Hester Lingsma, PhD, Teuntje M.J.C. Andriessen, MSc, Iain Haitsema, MD, Janneke Horn, MD, PhD, Joukje van der Naalt, MD, PhD, Gaby Franschman, MD, Andrew I.R. Maas, MD, PhD, Pieter E. Vos, MD, PhD, *and* **Ewout W. Steyerberg, PhD,** *Rotterdam, Netherlands*

BACKGROUND: Several prognostic models to predict outcome in traumatic brain injury (TBI) have been developed, but few are externally validated. We aimed to validate the International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic models in a recent unselected patient cohort and to assess the additional prognostic value of extracranial injury.

METHODS: The Prospective Observational COhort Neurotrauma (POCON) registry contains 508 patients with moderate or severe TBI, who were admitted in 2008 and 2009 to five trauma centers in the Netherlands. We predicted the probability of mortality and unfavorable outcome at 6 months after injury with the IMPACT prognostic models. We studied discrimination (area under the curve [AUC]) and calibration. We added the extracranial component of the Injury Severity Score (ISS) to the models and calculated the increase in AUC.

RESULTS: The IMPACT models had an adequate discrimination in the POCON registry, with AUCs in the external validation between 0.85 and 0.90 for mortality and between 0.82 and 0.87 for unfavorable outcome. Observed outcomes agreed well with predicted outcomes. Adding extracranial injury slightly improved predictions in the overall population (unfavorable outcome: AUC increase of 0.002, $p = 0.02$; mortality: AUC increase of 0.000, $p = 0.37$) but more clearly in patients with moderate TBI (unfavorable outcome: AUC increase of 0.008, $p < 0.01$, mortality: AUC increase of 0.012, $p = 0.02$) and patients with minor computed tomographic result abnormalities (unfavorable outcome: AUC increase of 0.013, $p < 0.01$; mortality: AUC increase of 0.001, $p = 0.08$).

CONCLUSION: The IMPACT models performed well in a recent series of TBI patients. We found some additional impact of extracranial injury on outcome, specifically in patients with less severe TBI or minor computed tomographic result abnormalities. (*J Trauma Acute Care Surg*. 2013;74: 639–646. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Epidemiologic/prognostic study,

KEY WORDS: Traumatic brain injury; trauma; prognosis; prognostic model; validation.

Traumatic brain injury (TBI) is a heterogeneous disease in terms of injury mechanism, pathological findings, severity, and prognosis,[1,2] which makes outcomes for individual patients difficult to predict.[3] Outcome prediction is however relevant for both clinical practice and research. Several prognostic models to predict outcome in TBI patients exist, but few meet the methodological requirements for valid prognostic model development, including a sufficiently large development sample and internal or external validation.[4,5] A set of prognostic models meeting these requirements is the International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT) models for the prediction of 6-month mortality and unfavorable outcome. These models were developed in almost 10,000 patients and include demographic variables (age), parameters of brain injury severity, computed tomographic (CT) findings and laboratory values as predictors.[6]

The IMPACT models have been externally validated and showed good performance beyond the development data.[7–9] Most of these validations required adaptation of the models or the use of an alternative outcome measure owing to data limitations, or they were performed in outdated studies. Prognostic models require continuous validation and updating, preferably in recent data. Such updating might also include testing of new predictors.

The IMPACT models do not contain information on injury to body parts other than the head, while multiple injuries are common in TBI patients, and extracranial injuries might affect prognosis. In the literature, the prognostic value of extracranial

Submitted: April 25, 2012, Revised: August 28, 2012, Accepted: August 30, 2012.
From the Departments of Public Health (H.L., E.W.S.) and Neurosurgery (I.H.), Center for Medical Decision Making, Erasmus Medical Center, Rotterdam, The Netherlands; Department of Neurology (T.M.J.C.A., P.E.V.), Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Department of Intensive Care Medicine (J.H.), Academic Medical Center, Amsterdam, the Netherlands; Department of Neurology (J.v.d.N.), University Medical Center Groningen, Groningen, the Netherlands; Department of Anesthesiology (G.F.), VU University Medical Center, Amsterdam, Amsterdam, the Netherlands; and Department of Neurosurgery (A.I.R.M.), University Hospital Antwerp, Antwerp, Belgium

Address for reprints: H.F. Lingsma, PhD, Center for Medical Decision Making, Department of Public Health, Erasmus MC, Rotterdam, PO Box 2040, 3000 CA, Rotterdam, the Netherlands; email: h.lingsma@erasmusmc.nl.

DOI: 10.1097/TA.0b013e31827d602e

injury in TBI is debated. Some studies have concluded that prognosis was mostly determined by the head injury, while others did find an independent prognostic effect of extracranial injury.[10] The Prospective Observational COhort Neurotrauma (POCON) study is a recently collected, unselected data set containing moderate and severe TBI patients admitted to a Level I trauma center in the Netherlands, including patients with multiple injuries.

The aims of this study were to validate the IMPACT prognostic models in a recent unselected patient cohort and to assess the additional prognostic value of extracranial injury.

PATIENTS AND METHODS

Study Population

The POCON study is an observational multicenter study of epidemiology, acute care, and outcome in the first year after moderate and severe TBI. The POCON database includes prospective data for all patients with moderate (Glasgow Coma Scale [GCS] score, 9–13) and severe (GCS score, 3–8) TBI admitted between June 1, 2008, and May 31, 2009, to one of the five specialized American College of Surgeons' Committee on Trauma (Level I) trauma centers in the Netherlands. The study protocol was approved by the local ethics committee of the coordinating hospital (Radboud University Nijmegen Medical Center). The other participating hospitals all provided a feasibility statement. For follow-up by telephone interview, verbal informed consent was obtained, and for outcome assessment through postal questionnaires, we obtained written informed consent.[11]

IMPACT Models

The IMPACT models were developed in the IMPACT database, which included prospectively collected data of moderate and severe TBI patients from eight randomized controlled trials (RCTs) and three observational series (total n = 8,509).[6] The IMPACT core model includes the predictors age, GCS motor score, and pupillary reactivity. The extended model added variables on secondary insults (hypoxia and hypotension) and CT scan characteristics (Marshall CT classification, traumatic subarachnoid hemorrhage, and epidural hematoma). Both models were developed for prediction of mortality and unfavorable outcome at 6 months.

Measures and End Points

The primary outcome of the POCON study was the Glasgow Outcome Scale Extended (GOSE), an 8-point scale ranging from death to complete recovery. For comparison with the IMPACT data and model validation, the GOSE was collapsed into the 5-point Glasgow Outcome Scale (GOS) and dichotomized in favorable (good recovery and moderate disability) versus unfavorable (dead, vegetative state, and severe disability) as well as in death versus alive. All predictors used in the IMPACT models were collected in the POCON registry, in a comparable way. When patients were intubated during GCS assessment, the variable GCS score was recoded into "untestable."

The severity of extracranial injury was expressed as the Injury Severity Score (ISS). The ISS is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an Abbreviated Injury Scale (AIS) score and is allocated to one of six body regions (head, face, chest, abdomen, extremities, and external). Only the highest AIS score in each body region is used. The three most severely injured body regions have their score squared and added together to produce the ISS score. The ISS ranges from 0 to 75.[12] Since we were interested in the additional prognostic value of extracranial injury, we calculated an extracranial ISS, for which the head AIS score was excluded.

Statistical Analyses

Patients with missing outcome were excluded. Patients' baseline characteristics were described as standard summary statistics, that is, median and interquartile range for continuous variables and frequencies and percentages for categorical variables. Because of the unselected nature of the POCON study, we also made a comparison with the IMPACT observational studies only. To assess the contribution of different "building blocks of prognosis" to the explained variance in outcome, we calculated the univariable and cumulative Nagelkerke R^2, indicating the variance explained by the model,[13] for sets of predictors (demographics, clinical severity, second insults, CT characteristics, and laboratory values) in IMPACT and POCON.

The external validity of the models was assessed by studying discrimination and calibration. Calibration refers to the agreement between observed and predicted outcomes. The extent of overestimation or underestimation relative to the observed and predicted rate was explored graphically using validation plots. We assessed calibration in the large by fitting a logistic regression model with the model predictions as an offset variable. The intercept indicates whether predictions are systematically too low or too high and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and was estimated in a logistic regression model with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1.

The area under the receiver operating characteristic curve (AUC) was used to assess the ability of the model to discriminate between death and survival or favorable and unfavorable outcome. AUCs of the refitted models were corrected for optimism by internal validation through bootstrap resampling (500 samples).[14] Based on 500 bootstrap samples, 95% confidence intervals of AUCs were also computed.

To study the additional prognostic value of extracranial ISS, we first assessed the shape of the relationship between extracranial ISS and outcome, by modeling ISS as a (univariable) restricted cubic spline with three knots.[14] We refitted the IMPACT laboratory model in the POCON data and consequently added extracranial ISS as predictor. We calculated the increase in AUC and the p value from the likelihood ratio test for improvement of goodness of fit. We studied the additional value of extracranial injury in the total population and separately in predefined TBI severity subgroups based on GCS score and CT classification.

The statistical analyses were preformed in R version 2.10 statistical software (R Foundation, Vienna, Austria). Missing values in the predictors were statistically imputed using single

TABLE 1. Baseline Characteristics of Patients the IMPACT and POCON Database

Characteristics	Measure or Category	Impact Total Database (n = 8,509)	Impact Observational Studies (n = 2,217)	POCON Database (n = 415)
Age, y	Total	8,509 (100%)	2,217	415 (100%)
	Median (25–75 percentile)	30 (21–45)	32 (22–53)	48 (29–67)
Motor score of GCS score	Total	8,509 (100%)	2,217	415 (100%)
	None (1)	1,395 (16%)	636 (29%)	114 (52%)
	Extension (2)	1,042 (12%)	399 (18%)	6 (1%)
	Abnormal flexion (3)	1,085 (13%)	272 (12%)	4 (1%)
	Normal flexion (4)	1,940 (23%)	166 (7%)	29 (7%)
	Localizes/obeys (5/6)	2,591 (30%)	376 (17%)	114 (27%)
	Untestable/missing (9)	456 (5%)	368 (17%)	48 (12%)
Pupillary reactivity	Total	7,126	2,090	396 (95%)
	Both pupils reactive	4,486 (63%)	1,190 (57%)	264 (67%)
	One pupil reactive	885 (12%)	231 (11%)	30 (8%)
	No pupil reactive	1,754 (25%)	669 (32%)	102 (26%)
Hypoxia	Total	5,452	2,195	392 (94%)
	Yes or suspected	1,116 (20%)	539 (25%)	90 (22%)
Hypotension	Total	6,420	2,202	408 (98%)
	Yes or suspected	1,171 (18%)	547 (25%)	85 (21%)
CT classification	Total	5,192	806	398 (96%)
	I	360 (7%)	98 (12%)	82 (21%)
	II	1,838 (35%)	226 (28%)	128 (32%)
	III	863 (17%)	81 (10%)	37 (9%)
	IV	187 (4%)	21 (3%)	4 (1%)
	V	1,435 (28%)	209 (26%)	88 (22%)
	VI	509 (10%)	171 (21%)	59 (15%)
Traumatic subarachnoid hemorrhage	Total	7,393	1,308	393 (95%)
	Yes or suspected	3,313 (45%)	554 (42%)	185 (47%)
Epidural hematoma	Total	7,409	1,577	393 (95%)
	Yes or suspected	999 (13%)	186 (12%)	47 (12%)
Glucose, mmol/L	Total	4,830	0	388 (94%)
	Median (25–75 percentile)	8.2 (6.7–10.4)	NA	8.1 (6.7–10.6)
Hemoglobin, g/dL	Total	3,871	0	397 (95%)
	Median (25–75 percentile)	12.6 (10.8–14.2)	NA	12.7 (11.1–13.8)
ISS	Total	0	0	406 (98%)
	Median (25–75 percentile)	NA	NA	25 (16–32)
ISS extracranial	Total	0	0	388 (94%)
	Median (25–75 percentile)	NA	NA	4 (1–26)
AIS face	Total	0	0	378
	≥3	NA	NA	13 (3%)
AIS chest	Total	0	0	376
	≥3	NA	NA	115 (31%)
AIS abdomen	Total	0	0	379
	≥3	NA	NA	18 (5%)
AIS extremities	Total	0	0	379
	≥3	NA	NA	58 (15%)
AIS external	Total	0	0	379
	≥3	NA	NA	2 (1%)
6-mo outcome	Dead	2,396 (28%)	904 (41%)	169 (41%)
	Vegetative	351 (4%)	65 (3%)	2 (0%)
	Severe disability	1,335 (16%)	364 (16%)	57 (14%)
	Moderate disability	1,666 (20%)	393 (18%)	83 (20%)
	Good recovery	2,761 (32%)	491 (22%)	104 (25%)

NA, not available.

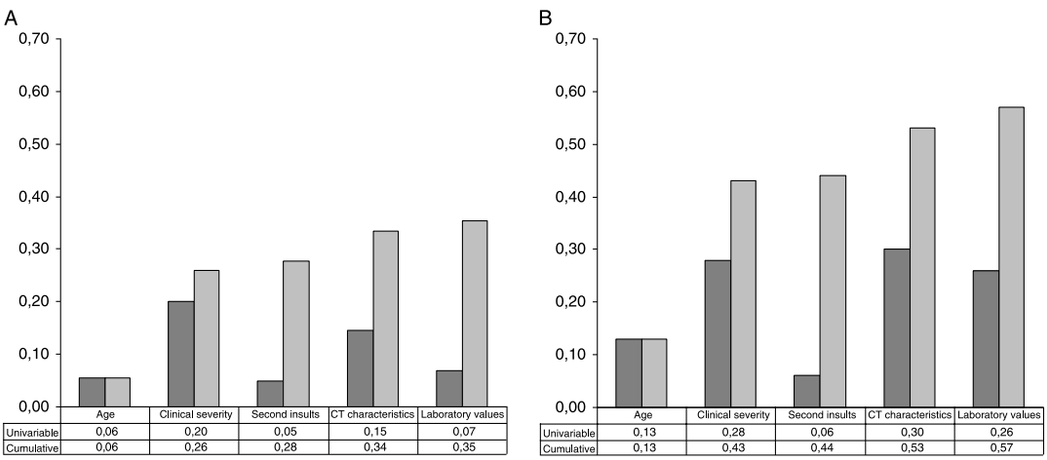

Figure 1. Explained variance (R^2) in unfavorable outcome by different ''building blocks of prognosis'' in IMPACT (*A*, n = 3,445) and POCON (*B*, n = 415). *Dark bars* represent the variance explained by each building block; *light bars* represent the cumulative explained variance.

imputation with the *aregImpute* function; the calibration plots were created with an adapted version of the *val.prob function*, both from Harrell's *rms* library.

RESULTS

Comparison of IMPACT and POCON

A total number of 508 patients were included in POCON. Of these, 93 had missing 6-month outcome and were excluded, leaving 415 patients for the analysis. There were few missing values in the predictors. Of the 4,565 data points (11 predictors used in 415 patients), 182 (4%) were missing. The highest percentage of missing values in a single predictor was 6% for glucose and extracranial ISS (Table 1).

Mortality was higher in the POCON study (41%) than in the total IMPACT database (28%) but exactly the same as in the IMPACT observational studies. The POCON patients were on average older (median age, 48 years vs. 30 years) and more often had an absent motor score (52% vs. 16%). More patients in the POCON study had a CT classification of I (21%) compared with the IMPACT data (7%). With regard to the other predictors, the study populations were largely similar (Table 1).

The total amount of variance in outcome explained by all predictors was higher in POCON ($R^2 = 0.57$) than in IMPACT ($R^2 = 0.35$, Fig. 1). The prognostic value of CT characteristics and laboratory values was higher in POCON than in IMPACT, while the prognostic value of clinical severity was relatively high in IMPACT.

Model Validation

The IMPACT models discriminated adequately in the POCON data; the AUCs in external validation varied from 0.85 to 0.90 for mortality and from 0.82 to 0.87 for unfavorable outcome (Table 2). For all models, discrimination was higher than in the development data, and there were minimal or even no differences in AUCs between the refitted models and the external validation.

Calibration was also adequate (Fig. 2, not all models shown). The calibration intercepts, which indicate the agreement between the mean observed and the mean predicted probability, were close to zero for most models. Small exceptions were the core model, which overestimated the mean probability on unfavorable outcome (intercept = −0.38), and the laboratory model, which underestimated the mean probability on mortality (intercept = +0.72). The calibration slopes, reflecting

TABLE 2. Discrimination (AUC) and 95% Confidence Intervals in the Development (IMPACT) and Validation (POCON) Data for Models Predicting Mortality and Unfavorable Outcome

	Core Model Mortality	Extended Model Mortality	Laboratory Model Mortality
Development	0.77 (0.75–0.78) (n = 8,509)	0.81 (0.80–0.82) (n = 6,999)	0.79 (0.77–0.81) (n = 3,554)
External validation	0.85 (0.81–0.88) (n = 415)	0.88 (0.85–0.91) (n = 415)	0.90 (0.87–0.92) (n = 415)
Refitted	0.85 (0.81–0.88) (n = 415)	0.89 (0.88–0.93) (n=415)	0.90 (0.89–0.94) (n = 415)
	Core Model, Unfavorable Outcome	**Extended model Unfavorable Outcome**	**Laboratory Model Unfavorable Outcome**
Development	0.78 (0.77–0.79) (n = 8,509)	0.81 (0.80–0.82) (n = 6,999)	0.81 (0.79–0.82) (n = 3,554)
External validation	0.82 (0.79–0.86) (n = 415)	0.85 (0.82–0.89) (n = 415)	0.87 (0.83–0.90) (n = 415)
Refitted	0.82 (0.79–0.86) (n = 415)	0.86 (0. 84–0.91) (n = 415)	0.87 (0.85–0.91) (n = 415)

Development, AUC in the development sample; external validation, AUC of model with original coefficients in validation sample; refitted, optimism corrected AUC of model with coefficients optimized (refitted) for the validation sample.

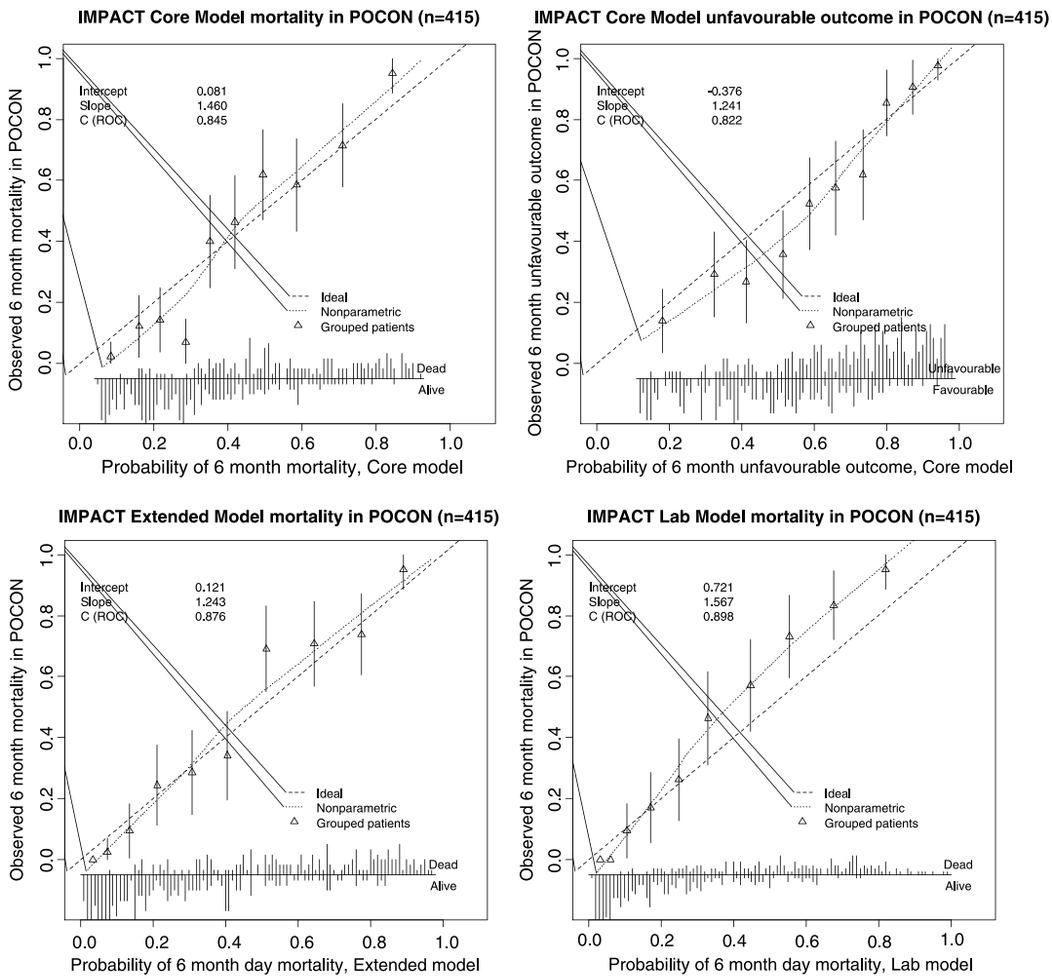

Figure 2. Calibration plots.

the overall strength of the prognostic effects, were close to 1. The relatively poorest calibration slopes were for the core model mortality (slope = 1.46) and unfavorable outcome (slope = 1.24) as well as the extended model for mortality (slope = 1.24) and the laboratory model for mortality (slope = 1.57).

Extracranial Injury

The median ISS in the POCON data was 25 (interquartile range, 16–32; Table 1). When head AIS score was excluded, the median extracranial ISS was 4 (interquartile range, 1–26). The overall prognostic value of extracranial ISS alone was limited (Fig. 3). The AUC of a model with extracranial ISS as the only predictor was 0.57 for unfavorable outcome and 0.54 for mortality. The relationship between extracranial ISS and outcome was approximately linear, and therefore, it was modeled as a linear term.

Adding extracranial ISS to the (refitted) IMPACT laboratory model showed that the added prognostic value in the overall population was small (AUC increase of 0.004, $p = 0.02$ for unfavorable outcome and AUC increase of 0.000, $p = 0.37$ for mortality; Table 3). In the subgroups of patients with severe TBI and a CT classification of III to VI, the additional value of extracranial ISS was even smaller (nonsignificant AUC increases of 0.000–0.001). In contrast, information on extracranial ISS did add prognostic value in moderate TBI (unfavorable outcome: AUC increase of 0.008, $p < 0.01$; mortality: AUC increase of 0.012, $p = 0.02$) and in patients with minor CT result abnormalities (CT Classifications I–II) (unfavorable outcome: AUC increase of 0.013, $p < 0.01$; mortality: AUC increase of 0.001, $p = 0.08$).

DISCUSSION

The IMPACT models performed well in the POCON data, both in terms of calibration and discrimination. Extracranial injury added no prognostic value in the overall patient population. However, in subgroups with less severe intracranial injury (moderate TBI based on the GCS score or CT Classification I or II), there was some additional prognostic value of extracranial injury.

The observed outcomes in POCON were worse than in IMPACT. More patients died, and fewer patients made a good recovery. Most patients in IMPACT were however included in RCTs with strict selection criteria, which may result in better outcomes. When comparing the observed outcomes in POCON

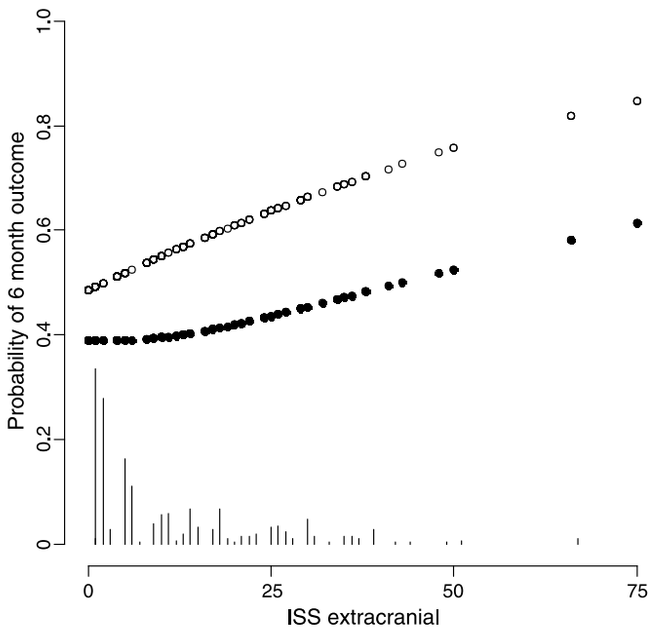

Figure 3. Relationship between ISS and outcome in POCON data On the *x* axis, ISS excluding head AIS score; on the *y* axis, the probability of mortality (*solid points*) and unfavorable outcome (*open points*). The distribution of patients over the ISS is displayed at the bottom.

with those in the observational studies in IMPACT, we found that observed outcomes were similar. This confirms the notion that RCTs enroll patients selectively. From the calibration plots, we observe that when the outcomes were adjusted for patient characteristics, they actually were very similar between POCON and the total IMPACT population; predicted outcomes were close to observed outcomes. This confirms the validity of the IMPACT model. It also implies that there has been limited improvement in outcome of TBI over recent years. This finding is in line with a meta-analysis conducted by Stein et al.[15] (2010), which showed a steady decline of mortality of approximately 9% per year during the period 1970 to 1990 but no change in mortality rates between 1990 and 2005.

We observed some remarkable differences in patient characteristics between POCON and IMPACT. The POCON patients were on average older than the IMPACT patients. This is likely caused by the changing epidemiology of TBI; from younger patients involved in road traffic accidents in the IMPACT studies from the 80s and 90s, toward more elderly patients experiencing falls in the recent years.[2] POCON patients more often had no motor reaction to painful stimuli (motor score = 1) and a CT classification of I. An explanation for the high number of patients with no or little CT pathologic diagnosis might be that POCON included patients with GCS score of 3 to 13, while IMPACT includes GCS score of 3 to 12. Since the combination of many CT Classification I patients and many absent motor scores seem to be contradictory, we expect part of the absent motor scores to be "false," that is, owing to intubation or sedation. Of the severe TBI patients in POCON, 75% was intubated at the moment the GCS score was assessed at the emergency department.[11]

Intubation and sedation complicate assessment of the GCS score and might constitute its prognostic value, which might be an explanation of the relatively low prognostic value of brain injury severity in POCON compared with the older IMPACT studies. The total amount of variance in outcome explained by all predictors was higher in POCON than in IMPACT, which is caused by the more heterogeneous population in POCON.[16]

Overall, the external validity of the prognostic models was very good, which is consistent with previous validations of the IMPACT models.[7–9] Our study primarily assesses the validity in a recent unselected patient cohort and furthermore assesses the additional prognostic value of extracranial injury. We found that discrimination was even better in the validation sample than in the development sample. This is caused by the more heterogeneous, unselected patient population in POCON, compared with the selected RCTs in IMPACT.[16] In heterogeneous patient populations, predicted outcomes are more extreme, which results in higher AUC, even if the model fit is exactly the same for two populations. A better indication for the good external

TABLE 3. The Added Value of Extracranial ISS Over the IMPACT Laboratory Models

Patients	Laboratory Model	Laboratory Model + Extracranial ISS	Increase	*p*
Mortality				
Total (n = 415)	0.917	0.917	0.000	0.37
Severe (n = 289)	0.923	0.923	0.000	0.91
Moderate (n = 126)	0.917	0.929	0.012	0.02
CT Classification I/II (n = 216)	0.916	0.917	0.001	0.08
CT Classification III/IV/V/VI (n = 199)	0.849	0.850	0.001	0.84
Unfavorable outcome				
Total (n = 415)	0.894	0.898	0.004	0.02
Severe (n = 289)	0.914	0.916	0.002	0.18
Moderate (n = 126)	0.869	0.887	0.008	<0.01
CT Classification I/II (n = 216)	0.855	0.868	0.013	<0.01
CT Classification III/IV/V/VI (n = 199)	0.852	0.852	0.000	0.66

Added value is expressed in AUC increase for the total population and in subgroups.

validity is therefore the minimal or even absent difference between the refitted AUCs, which represent the maximum achievable discrimination with the predictors included in the model.

Given the good external validity of the IMPACT models, we would recommend the use of these models in clinical practice and research. The main research applications of prognostic models in TBI are in classification of patient populations based on their prognostic risk and in the design and analysis of clinical trials.[17] In clinical practice, prognostic models could be used for quality assessment of health care delivery. Comparison of observed and expected outcomes may give an indication of the quality of care delivered in a specific hospital or in a specific country. The models might also be used for informing relatives, making treatment decisions or allocating resources, but caution is advocated when prognostic models are applied in individual patients. Prognostic estimates are probabilities and cannot provide certainty on an actual outcome.

The added prognostic value of extracranial injury was limited in the overall population but more pronounced in patients with relatively mild head injury, based on either GCS score (GCS score > 9) or on CT pathologic diagnosis (CT Classification I or II). This finding is supported by the literature. van Leeuwen et al.[10] reported in an individual patient meta-analysis that the prognostic effect of extracranial injury interacts with brain injury severity, with larger effects in milder TBI patient populations. In severe TBI, outcome is mostly determined by the brain injury, while in less severe TBI, patients are less likely to die of their brain injury, but the presence of extracranial injury might still cause poor outcome. Indeed, previous studies demonstrating that outcome is not worsened by extracranial injury only included severe TBI patients admitted to an intensive care unit,[18,19] while studies showing an effect of extracranial injury included also relatively mild TBI.[20–22]

Although the overall prognostic value of extracranial injury is limited, ISS measurement is relatively easy, essentially free of costs, and part of the standard diagnostic process in trauma care. Given this trade-off, inclusion of ISS in future prognostic models for TBI could be considered, dependent on the population under study and the setting in which the model is used.

Our study has some limitations. First, follow-up information was missing in 93 patients. These patients were on average somewhat younger and had less severe injury than the patients with follow-up information. This might have led to bias toward poor outcome in the study population. Second, we validated only the IMPACT models, while other prognostic models for moderate and severe TBI have been published. Specifically, the CRASH model is available, which does include extracranial injury.[21] Third, the validation sample was relatively small, while for external validation—as well as for model development—larger sample sizes are preferred.[23]

We calculated the extracranial ISS by excluding the head AIS score from the computation of the ISS. However, the head AIS score does represent not only intracranial damage but also maxillofacial en craniofacial injuries, which are common in TBI patients, and may cause complications and adversely affect outcome. It could be argued that these facial injuries should also be considered as extracranial injuries, but they are not included in our extracranial ISS, which may have resulted in underestimation of the prognostic value of extracranial injury.

In conclusion, our study has confirmed the broad generalizability of the IMPACT models. Their external validity has now been shown in several validation studies, and we recommend the use of these models in clinical practice and research. One should be aware however that in patients with less severe TBI and severe extracranial injuries, the prognosis estimated by the IMPACT models might be too optimistic.

AUTHORSHIP

H.L. performed the statistical analyses and wrote the article. T.M.J.C.A. coordinated the study and participated in the statistical analyses. E.W.S. supervised the statistical analyses. J.H., J.V.D.N., G.F., and I.H. acquired the data. A.I.R.M. and P.E.V. had the original idea for the study and acquired the funding. In addition, all authors contributed to the scientific content of the study and critically reviewed the article.

ACKNOWLEDGMENT

The POCON study is funded by the Dutch Brain Foundation (Hersenstichting, HSN-07-01). We thank Dick Drost, Annemiek Coers, Annelou van der Veen, Joshua Field, and Vivian de Ruijter for their help with the data collection. We thank Amon Heijne for his help with the development and maintenance of the POCON database and Carel Gosling (Trauma Unit AMC) for providing us with emergency department admission data.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Ghajar J. Traumatic brain injury. *Lancet*. 2000;356:923–929.
2. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol*. 2008;7:728–741.
3. Lingsma HF, Roozenbeek B, Steyerberg EW, Murray GD, Maas AI. Early prognosis in traumatic brain injury: from prophecies to predictions. *Lancet Neurol*. 2010;9:543–554.
4. Perel P, Edwards P, Wentz R, Roberts I. Systematic review of prognostic models in traumatic brain injury. *BMC Med Inform Decis Mak*. 2006;6:38.
5. Mushkudiani NA, Hukkelhoven CW, Hernandez AV, Murray GD, Choi SC, Maas AI, et al. A systematic review finds methodological improvements necessary for prognostic models in determining traumatic brain injury outcomes. *J Clin Epidemiol*. 2008;61:331–343.
6. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med*. 2008;5:e165; discussion e165.
7. Roozenbeek B, Lingsma HF, Lecky FE, Lu J, Weir J, Butcher I, et al. 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*. 2012;40:1609–1617.
8. Roozenbeek B, Chiu YL, Lingsma HF, Gerber LM, Steyerberg EW, Ghajar J, et al. Predicting 14-day mortality after severe traumatic brain injury: application of the IMPACT models in the brain trauma foundation TBI-trac New York State database. *J Neurotrauma*. 2012; pp 133–135.
9. Panczykowski DM, Puccio AM, Scruggs BJ, Bauer JS, Hricik AJ, Beers SR, et al. Prospective independent validation of IMPACT modeling as a prognostic tool in severe traumatic brain injury. *J Neurotrauma*. 2012;29:47–52.
10. van Leeuwen N, Lingsma HF, Perel P, Lecky F, Roozenbeek B, Lu J, et al. Prognostic individual patient data meta-analysis in 39 274 patients. *Neurosurgery*. 2012;70:811–818.

11. Andriessen TM, Horn J, Franschman G, van der Naalt J, Haitsma I, Jacobs B, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma*. 2011;28:2019–2031.
12. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14:187–196.
13. McHugh GS, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, Marmarou A, et al. Statistical approaches to the univariate prognostic analysis of the IMPACT database on traumatic brain injury. *J Neurotrauma*. 2007;24:251–258.
14. Steyerberg EW. *Clinical Prediction Models. A Practical Approach to Developement, Validating and Updating*. New York, NY: Springer; 2009.
15. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma*. 2010;27:1343–1353.
16. Vergouwe Y, Moons KG, Steyerberg EW. External validity of risk models: use of benchmark values to disentangle a case-mix effect from incorrect coefficients. *Am J Epidemiol*. 2010;172:971–980.
17. Roozenbeek B, Lingsma HF, Maas AI. New considerations in the design of clinical trials for traumatic brain injury. *Clin Investig (Lond)*. 2012;2:153–162.
18. Heinzelmann M, Platz A, Imhof HG. Outcome after acute extradural haematoma, influence of additional injuries and neurological complications in the ICU. *Injury*. 1996;27:345–349.
19. Sarrafzadeh AS, Peltonen EE, Kaisers U, Kuchler I, Lanksch WR, Unterberg AW. Secondary insults in severe head injury—do multiply injured patients do worse? *Crit Care Med*. 2001;29:1116–1123.
20. Lefering R, Paffrath T, Linker R, Bouillon B, Neugebauer EA; Deutsche Gesellschaft fur Unfallchirurgie/German Society for Trauma Surgery. Head injury and outcome—what influence do concomitant injuries have? *J Trauma*. 2008;65:1036–1043; discussion 1043–1044.
21. MRC CRASH Trial Collaborators, Perel P, Arango M, Clayton T, Edwards P, Komolafe E, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ*. 2008;336:425–429.
22. Jacobs B, Beems T, Stulemeijer M, van Vugt AB, van der Vliet TM, Borm GF, et al. Outcome prediction in mild traumatic brain injury: age and clinical variables are stronger predictors than CT abnormalities. *J Neurotrauma*. 2010;27:655–668.
23. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol*. 2005;58:475–483.