Validation of the CRASH model in the prediction of 18-month mortality and unfavorable outcome in severe traumatic brain injury requiring decompressive craniectomy

Clinical article

Stephen Honeybul, F.R.C.S., F.R.A.C.S.,¹ Kwok M. Ho, F.C.I.C.M., Ph.D.,² Christopher R. P. Lind, F.R.A.C.S.,¹,³ and Grant R. Gillett, F.R.A.C.S., D.Phil.⁴

¹Department of Neurosurgery, Sir Charles Gairdner Hospital and Royal Perth Hospital; ²Department of Intensive Care Medicine and School of Population Health, and ³School of Surgery, University of Western Australia, Perth, Western Australia, Australia; and ⁴Dunedin Hospital and Otago Bioethics Centre, University of Otago, Dunedin, New Zealand

Object. The goal in this study was to assess the validity of the corticosteroid randomization after significant head injury (CRASH) collaborators prediction model in predicting mortality and unfavorable outcome at 18 months in patients with severe traumatic brain injury (TBI) requiring decompressive craniectomy. In addition, the authors aimed to assess whether this model was well calibrated in predicting outcome across a wide spectrum of severity of TBI requiring decompressive craniectomy.

Methods. This prospective observational cohort study included all patients who underwent a decompressive craniectomy following severe TBI at the two major trauma hospitals in Western Australia between 2004 and 2012 and for whom 18-month follow-up data were available. Clinical and radiological data on initial presentation were entered into the Web-based model and the predicted outcome was compared with the observed outcome. In validating the CRASH model, the authors used area under the receiver operating characteristic curve to assess the ability of the CRASH model to differentiate between favorable and unfavorable outcomes.

Results. The ability of the CRASH 6-month unfavorable prediction model to differentiate between unfavorable and favorable outcomes at 18 months after decompressive craniectomy was good (area under the receiver operating characteristic curve 0.85, 95% CI 0.80–0.90). However, the model’s calibration was not perfect. The slope and the intercept of the calibration curve were 1.66 (SE 0.21) and -1.11 (SE 0.14), respectively, suggesting that the predicted risks of unfavorable outcomes were not sufficiently extreme or different across different risk strata and were systematically too high (or overly pessimistic), respectively.

Conclusions. The CRASH collaborators prediction model can be used as a surrogate index of injury severity to stratify patients according to injury severity. However, clinical decisions should not be based solely on the predicted risks derived from the model, because the number of patients in each predicted risk stratum was still relatively small and hence the results were relatively imprecise. Notwithstanding these limitations, the model may add to a clinician’s ability to have better-informed conversations with colleagues and patients’ relatives about prognosis.

Key Words • corticosteroid randomization after significant head injury prediction model • decompressive craniectomy • outcome • traumatic brain injury

The role of decompressive craniectomy in the management of severe traumatic brain injury (TBI) remains controversial.¹²,¹⁶,³⁰ Although there would appear to be little doubt that in the context of intractable intracranial hypertension, surgical decompression can reduce mortality rates,¹⁶,²² the evidence that the overall neurological outcome can be improved has been less forthcoming. The DECRA (decompressive craniectomy) study³ failed to show that early decompression provided clinical benefit, and the ongoing RESCUEIcp (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure) trial¹⁵ is investigating the role of decompressive craniectomy for a higher and more prolonged raised intracranial pressure (ICP) threshold.

However, the interpretation of any study attempting to demonstrate an improvement in outcome following surgical intervention as opposed to medical therapy must be tempered with the realization that this approach does
not necessarily reflect clinical practice. In most centers a decompressive craniectomy is usually performed once all medical therapy has failed or is in the process of failing, and in this context it can be very difficult to randomize patients to continue medical therapy. Indeed, this problem was highlighted by the high cross-over rate from the medical to the surgical arm of the DECRA study. 24 Both 1132

An alternative approach to the assessment of clinical efficacy has arisen following recent advances in data collection and statistical analysis that has enabled researchers to develop sophisticated prognostic models based on large patient samples. The IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) model, which was developed from 8509 patients, focused on patients with moderate and severe TBI. 19,28 The corticosteroid randomization after significant head injury (CRASH) collaborators model 21 was developed from the data collected on the 10,000 patients in the CRASH trial. 24 Both models are available as Web-based applications that provide a predicted risk of 14-day and 6-month mortality rates in the CRASH and IMPACT models, respectively, and the likelihood of unfavorable outcome at 6 months. Similar to most neurosurgical studies, an unfavorable outcome is defined by the Glasgow Outcome Scale (GOS) as either severely disabled, in a vegetative state, or dead. 17

Previous studies have demonstrated that the predicted risk of an unfavorable outcome can be used as a surrogate index of injury severity, which can allow patients to be stratified accordingly. 11,13 Comparing the predicted outcome with the observed long-term outcome provides an objective assessment of the outcome following surgical intervention relative to the severity of injury and the expected outcome. In this study, we aimed to assess the predictive validity of the CRASH model in patients with severe TBI requiring decompressive craniectomy. Specifically, we aimed to assess whether this model was well calibrated in predicting mortality and unfavorable outcome at 18 months across a wide spectrum of severity of TBI requiring decompressive craniectomy, and whether the calibration was similar when applied to patients who required decompression for refractory intracranial hypertension or decompression following evacuation of a mass lesion.

Methods

Hospital ethics committee approval was obtained for this prospective observational cohort study. The data from two previous studies were combined with data that have been collected prospectively since 2009. 11,13 This study has included all patients who had undergone a decompressive craniectomy following severe TBI at the two major trauma hospitals in Western Australia between 2004 and 2012 and in whom 18-month follow-up data were available. These two major trauma hospitals are the only neurosurgical centers that provide adult neurotrauma services in Western Australia, and there is a vast geographical separation from other state capital cities. Both hospitals are part of a statewide neurosurgical service covered by 8 neurosurgical consultants. There is a centralized rehabilitation service providing both inpatient and outpatient rehabilitation services for all individuals with severe TBI. These hospitals serve a population of approximately 2.2 million.

Indications for Decompressive Craniectomy

The indications for a decompressive craniectomy were either following evacuation of a mass lesion such as an acute subdural hematoma or in the context of intractable intracranial hypertension due to diffuse cerebral swelling.

Following Evacuation of a Hematoma With Mass Effect. Most patients who are symptomatic due to a hematoma with mass effect are taken immediately to the operating room for emergency evacuation. As large a bony decompression as possible is performed within the confines of patient positioning. After the hematoma has been evacuated a duraplasty is usually performed, and the bone flap is not replaced if the brain is believed to be too swollen or if following placement of a pressure monitor the ICP remains consistently above 20 mm Hg after the bone flap is replaced. All patients are then taken to the ICU for a period of ICP monitoring.

Following Intractable Intracranial Hypertension. The management of diffuse cerebral swelling is based on the Brain Trauma Foundation guidelines. 7 This involves protocol-driven, stepwise administration of sedation, ventilation, and CSF drainage where possible. The aim of therapy is to maintain the ICP below 20 mm Hg and the cerebral perfusion pressure above 60 mm Hg. A decompressive craniectomy was usually considered if the ICP could not be maintained below 25 mm Hg despite maximal medical management. The ICU charts were reviewed to obtain the mean ICP during the 2 hours prior to surgery. A bifrontal decompression was performed if the cerebral swelling was distributed evenly between both hemispheres. When the cerebral swelling was predominantly in one hemisphere, a unilateral decompression was performed. The surgeries were designed to provide maximal decompression. In all cases the dura mater was opened (most commonly in a cruciate fashion), and when necessary a duraplasty was performed with either pericranium or a synthetic dural substitute.

Data Analysis and Outcome Assessment

The clinical data between 2004 and 2009 were collected retrospectively. Since 2009, the data have been collected prospectively as part of an ongoing observational cohort study. The baseline presentation data were entered into the CRASH collaborators outcome prediction model to obtain a percentage prediction of the mortality rate at 14 days and unfavorable outcome at 6 months. The clinical predictive variables required for the model are as follows: age, postresuscitation Glasgow Coma Scale (GCS) score, pupillary response, and presence of a major extracranial injury. The radiological predictive variables are the presence of petechial hemorrhage, subarachnoid blood, midline shift, unevacuated hematoma, and obliteration of the basal cisterns.

All radiology images stored on the centralized PACS (picture archiving and communications) were independently reviewed by a consultant neurosurgeon (S.H.), and
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the findings were verified by another consultant neurosurgeon (C.R.P.L.) who was blinded to the clinical data. The GOS score at 18 months after the injury was assessed by S.H. The evaluation was based on the occupational therapy, physiotherapy, and neuropsychological assessments that are routinely performed as part of the centralized rehabilitation service.

Statistical Analysis

In validating the CRASH model, we used area under the receiver operating characteristic (ROC) curve to assess the ability of the CRASH model to differentiate between favorable and unfavorable outcomes. An area under the ROC curve ≥ 0.80 was considered good and an area under the ROC curve ≥ 0.70 but < 0.80 was considered acceptable. An area under the ROC curve < 0.70 was considered unsatisfactory.

Calibration of a prognostic model indicates how well the predicted risks agree with the observed risks across the full spectrum of predicted risks, and is vital in assessing the utility of a prognostic model. To assess the calibration of the model, we used a calibration plot to compare the predicted and observed risks of unfavorable outcomes. The slope and intercept of the calibration curve were calculated. A calibration curve with a slope of 1 and an intercept of 0 indicated perfect calibration. If the slope of the curve is < 1, it indicates that the predicted risk of unfavorable outcome is too extreme, with the model tending to underestimate unfavorable outcome of the low-risk strata and to overestimate unfavorable outcome of the high-risk strata. Conversely, if the slope is > 1, this indicates that the predicted risks of unfavorable outcome are not sufficiently different across the risk strata. An intercept < 0 indicates that the predicted risks of unfavorable outcomes are systematically too high and an intercept > 0 indicates that the predicted risks of unfavorable outcomes are systematically too low. Because the intercept can be affected by the slope of the calibration curve, as a standard procedure the intercept reported in this study was estimated with the slope set to 1.

The calibration of the model in predicting mortality and unfavorable outcome at 18 months was also assessed by the Hosmer-Lemeshow chi-square statistics, with a p value < 0.05 suggestive of imperfect calibration. All statistical analyses were 2-tailed and performed by SPSS software (version 18; 2008, SPSS, Inc.). A p value < 0.05 was regarded as significant.

Results

A total of 3231 adults with neurotrauma were admitted to the adult neurosurgical service between the years 2004 and 2012 in Perth, Western Australia, and a decompressive craniectomy was performed in 270 cases. Of these, 144 patients had a decompressive craniectomy following the development of intractable intracranial hypertension and 126 had decompression following evacuation of an intracranial hematoma. The characteristics of the 270 patients included in this study are described in Table 1.

Outcome at 18-Month Follow-Up

At the 18-month follow-up, 117 patients (43.3%) had made a good recovery, 51 (18.9%) remained moderately disabled, 50 (18.5%) were severely disabled, 7 (2.6%) remained in a vegetative state, and 45 (16.7%) had died. Note that for the 10 patients who did not have an 18-month follow-up, their outcome on last clinical review was recorded as their eventual outcome.

By using the CRASH collaborators outcome prediction model it was possible to stratify patients according to injury severity. Comparing the prediction of an unfavorable outcome with the observed long-term outcome provides an objective assessment of the most likely outcome following surgical intervention (Figs. 1–3).

External Validation of the CRASH Outcome Prediction Model

The ability of the CRASH 6-month unfavorable prediction model to differentiate between unfavorable and favorable outcomes at 18 months after decompressive craniectomy was good (area under the ROC curve 0.85 (95%
CI 0.80–0.90). The model’s calibration was, however, not perfect (Fig. 4). The slope and the intercept of the calibration curve were 1.66 (SE 0.21) and −1.11 (SE 0.14), suggesting that the predicted risks of unfavorable outcomes were not sufficiently extreme or different across different risk strata and were systematically too high (or overly pessimistic), respectively. The Hosmer-Lemeshow chi-square statistic was 17 (p = 0.03), and this is consistent with a model with imperfect calibration. There was no difference between patients who required decompression after evacuation of mass lesion and those who required decompression to control refractory intracranial hypertension.

The CRASH 14-day mortality prediction model had a reasonable ability to differentiate between mortality and survival outcomes at 18 months after decompressive craniectomy (area under the ROC curve 0.79 (95% CI 0.72–0.86). The calibration of the CRASH prediction model was slightly better in predicting mortality than unfavorable outcomes. The slope and the intercept of the calibration curve were 0.84 (SE 0.14) and −1.27 (SE 0.19), suggesting that the predicted risks of mortality were more extreme than expected across different risk strata and were systematically too high (or overly pessimistic), respectively. The Hosmer-Lemeshow chi-square statistic was 6.7 (p = 0.57), suggesting that the mortality predictions were slightly better calibrated than the unfavorable outcome predictions.

**Discussion**

Prognostication is important when considering outcome, especially when considering a potentially life-saving but not necessarily restorative surgical intervention. What outcome actually constitutes an “unacceptable” one after a life-saving procedure remains a subject of debate; however, some consideration must always be given to an outcome that is most likely to be acceptable.
Validation of CRASH model

This study has demonstrated that the predicted risk of unfavorable outcome at 6 months is strongly associated with the observed overall outcome at 18 months.

**Outcome Prediction**

Traditionally, neurosurgeons have relied on individual clinical parameters such as age, the initial GCS score, and pupillary responses combined with a radiological assessment to guide clinical decisions and when counseling family members and surrogate decision makers regarding prognosis. By combining these individual parameters and providing a percentage prediction, the CRASH collaborators model can be used as a more objective surrogate index of injury severity. This allows patients to be stratified according to injury severity, and comparing the predicted risk with the observed long-term outcome provides an objective assessment of the most likely outcome following decompressive surgery.

Our results suggest that the predicted risk of unfavorable outcome had excellent discriminatory ability, which meant that a randomly selected patient with unfavorable outcome was associated with a much higher predicted risk of unfavorable outcome compared with another randomly selected patient who had a favorable outcome. This supports the notion that the CRASH prediction model is a reasonable tool to assess severity of TBI and could potentially be used to compare balance in baseline characteristics of different treatment arms of a clinical trial of TBI.

Future Directions

Notwithstanding the results of this study, there remain many unanswered questions regarding the role of decompressive craniectomy in the management of severe TBI. One possible factor that may have influenced the results is that the CRASH study recruited patients who had mild to moderate TBI, and the model may be more accurate for patients with severe TBI.

There may be at least two reasons. The first is that there would be an expected difference between the prediction of outcome at 6 months and the observed outcome at 18 months because patients generally improve with time, and this has been demonstrated by a number of studies. Second, there is a possible interaction between the effectiveness of decompressive craniectomy and severity of TBI. It is possible that decompressive craniectomy might have improved the outcome of the patients who had mild to moderate injury compared with no decompression in most patients recruited in the CRASH study.

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![Figure 3](image1.png)

**Fig. 3.** Bar graph showing the prediction of an unfavorable outcome at 6 months and the observed outcome at 18 months among the 126 patients who had undergone a decompressive craniectomy following evacuation of an intracranial mass lesion. Numbers within the bars in the chart represent absolute patient numbers.

![Figure 4](image2.png)

**Fig. 4.** Calibration plot stratified according to the indication for decompressive craniectomy.
TBI, and one of the most challenging of these would appear to be appropriate patient selection.

One of the problems with selecting patients based on raised ICP, especially in the context of diffuse cerebral swelling, is that the ICP is primarily a marker of end organ damage. It is essentially a reflection of a number of deleterious neurochemical cascades initiated at the time of injury, many of which can be amplified by secondary insults such as ischemia, and it is becoming increasingly apparent that the severity of the molecular response can vary between individuals. Predicting those patients who will develop a particularly severe pathophysiological response can be difficult, and would not seem to be based entirely on the severity of the primary brain injury. Indeed, examination of the data in Fig. 3 shows that intractable intracranial hypertension developed in patients with widely varying severity of primary brain injury.

What is really required is a more dynamic and tailored assessment of the developing pathophysiology so that patients who are more likely to develop the more uncontrollable cerebral swelling can be identified early, and appropriate therapy, both medical and surgical, can be instigated before irreversible neurological injury has occurred.

In an attempt to address this issue, various multimodal monitoring techniques have been developed that can obtain continuous data regarding a number of physiological and biochemical parameters. The aim of these monitors is to gather as much information as possible for an accurate assessment of the development and severity of secondary injuries, with a view to more targeted therapeutic intervention. However, it is becoming increasingly recognized that information obtained from a single modality that is interpreted independently from other physiological and metabolic parameters is unlikely to provide significant clinical benefit. In the same way that the CRASH and IMPACT models have combined individual prognostic indicators, what may now be required are advances in real-time data analysis and presentation to provide an individualized pathophysiological profile and perhaps identify those patients for whom decompression may provide some benefit.

Conclusions

Sophisticated prediction models appear to be valuable tools in the treatment of patients with severe TBI. The CRASH model is not adequate on its own for prediction of outcome, particularly for mild to moderate TBI. Although this is one of the largest series of patients with TBI who required decompressive craniectomy, the number of patients in each predicted risk stratum was still relatively small and hence the results were imprecise. Furthermore, this study was based on population data from Western Australia, and whether this is generalizable to other neurosurgical centers has yet to be established.

The interactions between the benefits of decompressive craniectomy and the severity of TBI may need to be assessed in future studies, and, as with many prognostic models in medicine, we expect the CRASH prediction model’s discrimination and calibration to continue to deteriorate with advances in medical care and that further recalibration or modification of the model will be required.

Disclosure

The authors declare that they have no conflicts of interest. Author contributions to the study and manuscript preparation include the following. Conception and design: Honeybul. Acquisition of data: Honeybul. Analysis and interpretation of data: Honeybul, Ho, Lind. Drafting the article: Honeybul. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Honeybul. Statistical analysis: Ho.

References

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Address correspondence to: Stephen Honeybul, F.R.C.S, F.R.A.C.S., Department of Neurosurgery, Sir Charles Gairdner Hospital, Hospital Ave., Perth, WA, Australia 6009. email: stephen.honeybul@health.wa.gov.au.