The application of adult traumatic brain injury models in a pediatric cohort

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OBJECTIVE There is increasing interest in the use of predictive models of outcome in adult head injury. Two international models have been identified to be reliable modalities for predicting outcome: the Corticosteroid Randomisation After Significant Head Injury (CRASH) model, and the International Mission on Prognosis and Analysis of randomized Controlled Trials in TBI (IMPACT) model. However, these models are designed only to identify outcomes in adult populations.

METHODS A retrospective analysis was performed on pediatric patients with severe traumatic brain injury (TBI) admitted to the pediatric intensive care unit (PICU) of Addenbrooke’s Hospital between January 2009 and December 2013. The individual risk of 14-day mortality was calculated using the CRASH-Basic and -CT models, and the risk of 6-month mortality calculated using the IMPACT-Core and -Extended (including CT findings) models. Model accuracy was determined by standardized mortality ratio (SMR; observed/expected deaths), discrimination was evaluated as the area under the receiver operating curve (AUROC), and calibration assessed using the Hosmer-Lemeshow χ² test.

RESULTS Ninety-four patients with an average age of 7.3 years were admitted to the PICU with a TBI. The mortality rate was 12.7% at 14 days and 6 months. For the CRASH-Basic model, the SMR was 1.42 and both calibration (χ² = 6.1, p = 0.64) and discrimination (AUROC = 0.92) were good. For the IMPACT-Core model, the SMR was 1.03 and the model was also well calibrated (χ² = 8.99, p = 0.34) and had good discrimination (AUROC = 0.85). Poor outcome was observed in 17% of the cohort and identified with the CRASH-Basic and IMPACT-Core models to varying degrees: standardized morbidity ratio = 0.89 vs 0.67, respectively; calibration = 6.5 (χ²) and 0.59 (p value) versus 8.52 (χ²) and 0.38 (p value), respectively; and discrimination (AUROC) = 0.92 versus 0.83, respectively.

CONCLUSIONS Adult head injury models may be applied with sufficient accuracy to identify predictors of morbidity and mortality in pediatric TBI.

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KEY WORDS brain; injury; acute; prediction; trauma

TRAUMATIC brain injury (TBI) remains a major public health problem.6 The early management phase of TBI aims to limit secondary insults, achieve hemodynamic stability, obtain accurate neurological assessment, and appropriately select patients for further investigation.10 Epidemiological studies demonstrate that the incidence of hospitalization and fatality in TBI is disproportionately high in adolescents. The Centers for Disease Control and Prevention reports more than 1.4 million incidents of TBI in children and in excess of 50,000 deaths annually related to the injury in the US.6 Insight into which factors determine prognosis after TBI is useful for clinical practice, research, and making policy. Several steps can be identified in prediction research: univariate analysis, multivariable analysis, and the development of prediction models.15 In identifying these steps, several issues need to be addressed, especially selection/coding of predictors of outcome.15 Due to the large
number of patients required to generate and validate re-
gression models, accurate prediction tools specific to pe-
diatric brain injury are difficult to develop and few have
been published.18

Prognostic models can be advantageous at both an
individual and group level. On an individual level they
complement clinical assessment and can be used, albeit
with caution, to support decisions on treatment, provide
information to relatives, and inform resource allocation.17
At a group level, prognostic models can be used to select
specific patient subgroups for enrollment in clinical tri-
als or to improve the power of outcome analyses, and im-
portantly, can serve as benchmarks for auditing quality of
care.15

Baseline predictors include age, sex, mechanism or type
of injury, clinical severity, extracranial injury, and the pres-
ence of structural abnormalities on neuroimaging.19

Two prognostic models for use in TBI, developed using
large patient databases, have been externally validated: the
International Mission on Prognosis and Analysis of ran-
domized Controlled Trials in TBI (IMPACT) model, and
the Corticosteroid Randomisation After Significant Head
Injury (CRASH) model.20 Both models have shown good
performance in external validations.21 Importantly, these
models were developed not only to predict mortality but
also to predict functional outcome.

Pediatric head injury remains heavily understudied,
and many of the current treatment protocols and inter-
ventions are derived from evidence in adult studies.22 Both
IMPACT and CRASH models were independently de-
signed to predict outcomes in adult populations. However,
we hypothesize that these models could be of potential
value in younger cohorts. In this study we have applied the
IMPACT and CRASH prediction models to a pediat-
ric cohort with severe TBI, reviewed over a 5-year period.
In this study we have applied the IMPACT and CRASH prediction models to a pediat-
ric cohort with severe TBI, reviewed over a 5-year period. This cohort has been analyzed to predict both mortality and poor outcome using the extended predictive models.

Methods

Study Population

The data in this study were collected retrospectively
from data records of pediatric patients with severe TBI
admitted to the pediatric intensive care unit (PICU) of Ad-
denbrooke’s Hospital between January 2009 and Decem-
ber 2013.

Inclusion criteria for the study were as follows: 1) con-
firmed TBI, using CT or MRI; 2) severe injury or failure
to demonstrate significant early clinical improvement (i.e.,
poor neurological condition while withholding sedation)
or an injury that required close conservative management
or neurological monitoring in the PICU; and 3) patients
requiring invasive monitoring of intracranial pressure or
arterial blood pressure.

Patients were managed according to current TBI guide-
lines.19 Interventions were aimed at keeping intracranial
pressure below 20 mm Hg using a tiered treatment pro-

Table 2. The median (± IQR) blood glucose measure-
ment was 6.8 ± 1.1 mmol/L with a median hemoglobin
level of 10.5 ± 1.8 g/dl.

The mortality rate was 13% at 14 days and at 6 months.
Of those who survived, 63% had a Glasgow Outcome
Scale (GOS) score of 5, 20% a GOS score of 4, and 4% a
poor but survivable outcome (3% a GOS score of 3, 1% a
GOS score of 2).

CRASH Discrimination Model

CRASH-Basic was demonstrated to be a reliable pre-
dictor for mortality, in which the SMIR = 1.42, and both
calibration ($\chi^2 = 6.1$, $p = 0.64$) and discrimination (AU-
ROC = 0.92) demonstrated a strong association (Fig. 1A).
The CRASH-CT model was also found to show a strong
association (SMIR = 0.82; calibration = 11.84 [$\chi^2$] and 0.16

Data Acquisition

Patient demographics and 6-month follow-up data were
obtained from electronic records. Serum marker levels
were extracted from admission blood tests. CT findings
were obtained from referring images to the Department
of Neurosurgery, Addenbrooke’s Hospital. Information on
admitting clinical features (such as Glasgow Coma Scale
[GCS] score, hypotension, and hypoxia) were obtained
from the PICU discharge summary. Outcome measures
were obtained from the patients’ 6-month clinic follow-up
documentation.

Statistical Analysis

Ordinal data are presented as medians with their in-
terquartile ranges (IQRs) and continuous data as means
and associated standard deviations. The individual risk
of 14-day mortality was calculated using CRASH-Basic
and -CT models, and risk of 6-month mortality calculated
with IMPACT-Core and -Extended (including CT find-
ings) models (Table 1). Model accuracy was determined
by standardized mortality ratio (SMIR; observed/expected
deaths), discrimination was evaluated as the area under
the receiver operating curve (AUROC), and calibration
assessed using the Hosmer-Lemeshow $\chi^2$ test. Statistics
were performed in R, in which $p < 0.05$ was considered
significant. Results were validated using the online calcu-
lators for each test.

Results

Ninety-four patients with an average age of 7.3 years
were admitted to the PICU with a TBI. The baseline cli-
nical features are outlined in Table 2. The modified Mar-
shall scores ranged from 1 to 5 with a mode of 2. Specific
CT features included subarachnoid hemorrhage in 39%
of patients and subdural and extradural hemorrhage in
10% and 13%, respectively. Of the extraaxial hemorrhages
identified, 43% were evacuated. Petechial hemorrhages
were observed in 21% of the cohort, with obliteration of
the basal cisterns also observed relatively infrequently
in 10% of the cohort. Midline shift was observed in 29%
(Table 2). The median (± IQR) blood glucose measure-
ment was 6.8 ± 1.1 mmol/L with a median hemoglobin
level of 10.5 ± 1.8 g/dl.

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Of those who survived, 63% had a Glasgow Outcome
Scale (GOS) score of 5, 20% a GOS score of 4, and 4% a
poor but survivable outcome (3% a GOS score of 3, 1% a
GOS score of 2).
5.44 demonstrated an SMtR of 0.93, as well as a calibration of AUROC; Fig. 3A). Finally, the IMPACT-Lab model was also well suited for mortality (SMtR = 1.07; calibration = 4.67 [p value]; discrimination = 0.89 [AUROC]; Fig. 2A). The IMPACT-Extended model was also well suited for mortality (SMtR = 0.55, calibration = 20.37 [p value]; discrimination = 0.91 [AUROC]; Fig. 1D).

### IMPACT Discrimination Model

The IMPACT models demonstrated improved ability to discriminate both mortality and morbidity in the pediatric cohort. For mortality, the IMPACT-Core model showed strong correlations (SMbR = 0.89; Fig. 2B). The IMPACT-Extended model was also well suited for mortality (SMtR = 1.07; calibration = 4.67 [p value]; discrimination = 0.87 [AUROC]; Fig. 3A). Finally, the IMPACT-Lab model demonstrated an SMtR of 0.93, as well as a calibration of 5.44 [p value] and 0.71 (p value), and a discrimination of 0.90 (AUROC; Fig. 3B).

Morbidity was equally well discriminated using the IMPACT models. The IMPACT-Core model demonstrated equally strong correlations (SMbR = 0.89; calibration = 8.52 [p value]; discrimination = 0.83 [AUROC]; Fig. 2B). The IMPACT-Extended model performed similarly (SMbR = 0.89; calibration = 6.95 [p value]; and 0.54 [p value]; discrimination = 0.87 [AUROC]; Fig. 3C). Finally the IMPACT-Lab model was also accurate at predicting poor outcome (SMbR = 0.83; calibration = 6.57 [p value] and 0.58 [p value]; discrimination = 0.88 [AUROC]; Fig. 3D).

### Discussion

In this study we have identified that both the CRASH and IMPACT scoring systems can be applied to a pediatric cohort. The models show positive features that indicate they can discriminate and are largely well calibrated. On this basis they can potentially be applied in pediatrics as long as their shortcomings are acknowledged. Predictive scoring systems are used both clinically and in research to varying degrees. Clinically, some estimation of prognosis is consciously or subconsciously used by physicians when informing relatives, making treatment decisions, or allocating resources. In modern-day practice, evidence derived from large data sets is held in greater regard than evidence from the subjective opinion of an individual. The Canadian CT rule and the CHIP (CT in head-injury patients) prediction rule for CT scanning in mild TBI are examples of how prediction models can provide evidence to better inform clinical decisions.

One of the greatest benefits of prognostic models for outcome in TBI is group stratification in data analysis and enrollment into clinical trials. Prognostic risk estimation on hospital admission enables populations to be classified according to their prognostic risk distribution. This is particularly useful in pediatrics given the significant heterogeneity among the cohort. We can therefore use such models to gain insight into differences in the case mix of different studies.

The application of the CRASH models demonstrated that they were reliable predictors of mortality when both CRASH-Basic and -CT models of the test were applied. Whereas CRASH-Basic was also able to predict morbidity in an accurate fashion, the CRASH-CT test was poorly calibrated by comparison. This is likely to be associated

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**TABLE 1. Components considered for both CRASH and IMPACT prediction models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRASH-Basic</td>
<td>Age, GCS score, pupils, &amp; major extracranial injury</td>
</tr>
<tr>
<td>CRASH-CT</td>
<td>CRASH-Basic variables, + petechial hemorrhage, obliteration of 3rd ventricle/basal cisterns, SAH, midline shift, &amp; nonevacuated hematoma</td>
</tr>
<tr>
<td>IMPACT-Core</td>
<td>Age, GCS score (motor), pupils</td>
</tr>
<tr>
<td>IMPACT-Extended</td>
<td>IMPACT-Core variables, + hypoxia, hypotension, Marshall CT, SAH, &amp; extradural hematoma</td>
</tr>
<tr>
<td>IMPACT-Lab</td>
<td>IMPACT-Extended variables, + hemoglobin &amp; glucose levels</td>
</tr>
</tbody>
</table>

**TABLE 2. Patient demographics used to calculate outcome scores**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>Mean age ± SD (yrs)</td>
<td>7.3 ± 5.1</td>
<td>7.5 ± 5.7</td>
</tr>
<tr>
<td>Males (%)</td>
<td>48 (59)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Median admission GCS score (range)</td>
<td>9 (3–13)</td>
<td>3 (3–9)</td>
</tr>
<tr>
<td>Median motor score (range)</td>
<td>6 (1–6)</td>
<td>1 (1–5)</td>
</tr>
<tr>
<td>Pupils (%)</td>
<td>Reactive</td>
<td>74 (90)</td>
</tr>
<tr>
<td></td>
<td>Fixed unilaterally</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>Fixed bilaterally</td>
<td>3 (4)</td>
</tr>
<tr>
<td></td>
<td>Prehospital hypoxia (%)</td>
<td>6 (7)</td>
</tr>
<tr>
<td></td>
<td>Prehospital hypotension (%)</td>
<td>6 (7)</td>
</tr>
<tr>
<td></td>
<td>Midline shift (%)</td>
<td>21 (26)</td>
</tr>
<tr>
<td></td>
<td>Surgical intervention (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>External ventricular drain</td>
<td>8 (10)</td>
</tr>
<tr>
<td></td>
<td>Hematoma evacuation</td>
<td>15 (18)</td>
</tr>
<tr>
<td></td>
<td>Decompression</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Mean hemoglobin ± SD (g/dl)</td>
<td>6.9 ± 1.9</td>
<td>10.8 ± 4.1</td>
</tr>
<tr>
<td>Mean glucose ± SD (mmol/L)</td>
<td>10.7 ± 1.8</td>
<td>11.2 ± 3.4</td>
</tr>
</tbody>
</table>
Fig. 1. CRASH model predictions of outcome in children. A: The CRASH-Basic model was demonstrated to be a reliable predictor for mortality, where SMtR = 1.42 with both calibration ($p = 0.64$) and discrimination (AUROC = 0.92) demonstrating a strong association with outcome. B: The CRASH-Basic model was also able to successfully predict poor outcome among patients (SMbR = 0.89, calibration [p value] = 0.59, discrimination [AUROC] = 0.92). C: The CRASH-CT model was observed to have a strong association with outcome: SMtR = 0.82, calibration [p value] = 0.16, discrimination [AUROC] = 0.89. D: The only test that failed to provide any predictive accuracy was the application of the CRASH-CT model in predicting poor outcome, in which the SMbR = 0.55, calibration (p value) = 0.01, and discrimination (AUROC) = 0.91. Figure is available in color online only.
with the fact that the CRASH predictive model does not calculate outcomes of patients with a GCS score of 15. Additionally, in this cohort we are extrapolating below the age of the patient group originally used to create the model. The age range for predicting outcomes in CRASH are collectively grouped for adults under the age of 40. The inference that adults between the ages of 18 and 40 would have a similar outcome demonstrates that this model in particular is weighted more toward the other variables measured. Given that this is not likely to be the case in a pediatric cohort and that the outcome will very much be age dependent, perhaps improving with increased age and subsequent development, it is reasonable to suspect these factors are responsible for the shortcomings in accuracy.

The IMPACT models performed slightly more favorably overall, with all 3 independently able to predict both morbidity and mortality. IMPACT-Extended and IMPACT-Lab both outperformed IMPACT-Core, which demonstrates the importance of the respective variables on outcome. The IMPACT calculator accounts for ages 14 years and older. The stratification of age into individual years in this manner may account for a better degree of discrimination and fit in these tests.

In this study we have successfully demonstrated that both CRASH and IMPACT analytical models can be used to predict outcomes in morbidity and mortality in a pediatric cohort. This is most applicable for the stratification of patient groups for the analysis of research into pediatric head injury. The pathophysiology of pediatric brain injury is relatively understudied despite large epidemiological studies demonstrating that the incidence of hospitalization and fatal brain injury is disproportionately high in children. The Centers for Disease Control and Prevention report more than 1.4 million incidents of TBI in children and in excess of 50,000 deaths related to the injury in the US. Understanding the intricacies of this condition and identifying areas where adult treatments could be used will depend on the careful selection of research groups, a particularly difficult task in pediatric TBI.

There were notable limitations to this study: the retrospective nature increases the possibility of missing data, and the sample size was modest but expected for a single center considering that only intensive care patients were included. To further investigate the findings from this study, a multicenter analysis of pediatric TBI would be beneficial. In this way, new variables could be introduced and less relevant ones excluded in such a way that a more specific model could be adapted. This study has demonstrated proof of concept that these models are appropriate and that this is an endeavor that would be worthwhile in a cohort of severely injured patients. Whether this will be similar in a mild to moderately injured cohort remains unclear.

**Conclusions**

Our observations have identified that both the CRASH

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**FIG. 2.** IMPACT model predictions of outcome in children. **A:** The IMPACT models demonstrated an improved ability to discriminate both mortality and morbidity in the pediatric cohort. For mortality, the IMPACT-Core model showed strong correlations (SMR = 1.03) and was well calibrated (p = 0.34) with good discrimination properties (AUROC = 0.85). **B:** Poor outcomes were equally well discriminated using the IMPACT models. The IMPACT-Core model demonstrated equally strong correlations: SMbR = 0.89, calibration (p value) = 0.38, discrimination (AUROC) = 0.83. Figure is available in color online only.
FIG. 3. IMPACT-Extended and -Lab model predictions of outcome in children. A: The IMPACT-Extended model was also well suited for mortality: SMtR = 1.07, calibration (p value) = 0.79, discrimination (AUROC) = 0.87. B: The IMPACT-Lab model demonstrated an SMtR = 0.93, calibration of 0.71 (p value), and discrimination of 0.90 (AUROC). C: The IMPACT-Extended model performed similarly in morbidity: SMbR = 0.89, calibration (p value) = 0.54, discrimination (AUROC) = 0.87. D: Finally, the IMPACT-Lab model was also accurate at predicting poor outcome: SMbR = 0.83, calibration (p value) = 0.58, discrimination (AUROC) = 0.88. Figure is available in color online only.
and IMPACT scoring systems can be applied to a pediatric cohort. As such, the outcome of pediatric head injury can be predicted with excellent discrimination and good fit using parameters available at the bedside. In an understudied patient group this will allow for improved group stratification in data analysis and enrollment into clinical trials. Although this study is limited by its modest sample size, it acts as a proof of concept model that these analytical tools can be applied to pediatric patients with TBI. Nevertheless, due to the sample size in the current cohort, external validation would be appropriate with a multicenter data set.

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References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Young, Guilfoyle. Acquisition of data: Young, Analysis and interpretation of data: Young, Guilfoyle, Hutchinson. Drafting the article: Young. Critically revising the article: Guilfoyle, Fernandes, Garnett, Agrawal, Hutchinson. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Young. Study supervision: Fernandes, Garnett, Agrawal, Hutchinson.

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