Early prognosis in traumatic brain injury: from prophecies to predictions

Hester F Lingsma, Bob Roozenbeek, Ewout W Steyerberg, Gordon D Murray, Andrew I R Maas

Traumatic brain injury (TBI) is a heterogeneous condition that encompasses a broad spectrum of disorders. Outcome can be highly variable, particularly in more severely injured patients. Despite the association of many variables with outcome, prognostic predictions are notoriously difficult to make. Multivariable analysis has identified age, clinical severity, CT abnormalities, systemic insults (hypoxia and hypotension), and laboratory variables as relevant factors to include in models to predict outcome in individual patients. Advances in statistical modelling and the availability of large datasets have facilitated the development of prognostic models that have greater performance and generalisability. Two prediction models are currently available, both of which have been developed on large datasets with state-of-the-art methods, and offer new opportunities. We see great potential for their use in clinical practice, research, and policy making, as well as for assessment of the quality of health-care delivery. Continued development, refinement, and validation is advocated, together with assessment of the clinical impact of prediction models, including treatment response.

Introduction

Prognosis is the cornerstone of clinical medicine, because all diagnostic and therapeutic actions aim to improve a patient’s prognosis and outcome. Advances in statistical modelling and the availability of large databases have made it possible to consider diagnosis and prognosis in terms of probabilities rather than vague prophecies. Probability estimates can be applied to clinical decision making, research, and assessment of the quality of health care. Such quantitative estimates are of particular relevance to heterogeneous conditions such as traumatic brain injury (TBI).

TBI poses a major public-health problem, with an estimated annual incidence of up to 500 per 100 000 population and more than 200 hospital admissions per 100 000 admissions in Europe each year. TBI is heterogeneous in terms of cause, pathology, severity, and prognosis, which poses diagnostic challenges. Furthermore, comparison of results between studies is difficult because case mix and treatments may vary substantially.

Various outcomes can be considered in prediction research. A diagnostic perspective is taken in TBI studies, and involves assessment of the probability of structural brain damage or developing an intracranial haematoma, or is used to underpin recommendations for CT scanning. For example, a recent study used a prediction rule to identify a subset of children who had such low risk for intracranial damage that CT scans were unnecessary. These types of diagnostic outcomes are particularly relevant for patients with mild TBI. The ability to predict response to treatment would be highly relevant to patients in the intensive-care setting, in whom intracranial pressure is monitored, but such prognostic rules have not yet been developed. For patients with moderate and severe TBI, prediction of clinical outcome is also highly relevant. Typically, most studies have defined clinical outcome as mortality or functional outcome assessed with the Glasgow outcome scale (GOS) as their endpoint.

In this Review, we focus on the prediction of outcome in terms of mortality and functional outcome in patients with moderate and severe TBI. We aim to describe the basics of prognostic analysis and review the current knowledge about traditional and newly recognised predictors for outcome in TBI. We also discuss prognostic modelling as a novel instrument in medicine, critically review prediction models in TBI, describe the applications for prognostic models in TBI, and provide suggestions for the further development and improvement of prediction research in TBI. We will use the term “outcome” to refer to all endpoints from different studies that use mortality and GOS.

Predictors of outcome

Much research has been done to identify early predictors of mortality and functional outcome, as assessed by the GOS on admission, after moderate or severe TBI. The GOS is usually dichotomised into good recovery and mild disability versus severe disability, vegetative state, and mortality. This is a limitation because we cannot assume that predictors differentiate death from survival as well as they can differentiate good recovery from worse outcomes.

A large body of evidence supports the relation between some predictors and outcome, but for other predictors the relation is less well established. Information obtained during the subsequent clinical course may further contribute to outcome prediction. An overview of the various components of prognostic analysis is shown in figure 1, which illustrates the complex relations between potential predictors and highlights gaps in our knowledge (eg, genomics, biomarkers).

Basics of prediction research

Several steps in prediction research have been identified (table I). First, the association between a single predictor and outcome can be studied by univariate analysis, relating a single predictor to the outcome of interest. Such
an analysis is of limited value because it does not take into account the role of other confounding factors that may explain (part of) the observed association. Statistical analyses, such as logistic regression, are therefore needed to adjust for confounders in the assessment of relative risks. Odds ratios (ORs) are commonly used to express the strength of prognostic effects. The relation is significant if the 95% CI for the OR does not include the value 1·0. However, the OR does not account for the prevalence of a predictor. A predictor with a high OR but a very low prevalence is thus of limited predictive value. Predictive value is better reflected in measures such as explained variation ($R^2$). Other statistical approaches to prognostic analysis include recursive partitioning (prediction trees) and neural network analysis.

### Admission characteristics

The prognostic strength of the main predictors of outcome in TBI is summarised in table 2. The prognostic value of the different characteristics was quantified in the International Mission for Prognosis and Clinical Trial design in TBI (IMPACT) study data (figure 2). Clinical severity had the highest prognostic value ($R^2$), followed by CT characteristics. Both measures were significant if included in the model separately and when they were added in the order of availability in clinical practice.

#### Demographic factors

Age is one of the strongest predictors of mortality and functional outcome in TBI; many studies have shown that older age is associated with poorer outcome.\[^{11-21}\] Most studies analysed the association between age and outcome by use of threshold values, varying from 30 to 60 years of age.\[^{11-16}\] Only a few studies have analysed the association between age and outcome in a continuous way; these studies report both a change around age 30–40 years, above which outcome becomes increasingly poorer, and a fairly continuous relation across all ages, which may be approximated by a linear function.\[^{17-21}\]

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**Table 1: Steps in prognostic analysis in traumatic brain injury**

<table>
<thead>
<tr>
<th>Aim</th>
<th>Limitations</th>
<th>Performance measures</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>To estimate the relation between a single predictor and outcome</td>
<td>Sensitivity, specificity, positive predictive value, negative predictive value, odds ratio</td>
<td>Tabular, graphical representation</td>
</tr>
<tr>
<td>Multivariable analysis</td>
<td>To determine the prognostic value of a predictor, adjusting for confounding effects of other predictors</td>
<td>Odds ratio, risk ratio, $R^2$</td>
<td>Tabular, graphical representation</td>
</tr>
<tr>
<td>Prediction models</td>
<td>To combine predictors into a model to estimate the risk of an outcome for individual patients</td>
<td>Discrimination: area under the receiver operating characteristic curve</td>
<td>Web-based calculator, score chart</td>
</tr>
</tbody>
</table>

Sensitivity = proportion of patients with the outcome that have the predictor (true positive). Specificity = proportion of patients without the outcome that do not have the predictor (true negative). Positive predictive value = proportion of patients with the predictor that have the outcome. Negative predictive value = proportion of patients without the predictor that do not have the outcome. Odds ratio = ratio of the odds for better versus poorer outcome in the presence of the variable, compared with the odds in the absence of the variable. Risk ratio = risk of outcome in group with the predictor versus group without the predictor. $R^2$ = proportion of variability in outcome that is explained by the predictor; $R^2$ indicates predictive value better than odds ratio does, because prevalence is also taken into account. Based on Steyerberg.8

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**Figure 1: Overview of the components of prognosis in traumatic brain injury**

GCS=Glasgow coma scale. AIS/ISS=abbreviated injury score/injury severity score. ICP=intracranial pressure. PO2=partial pressure of oxygen.
Other demographic factors, such as sex and ethnic origin, are also associated with outcome after TBI. Men are more likely to have TBI owing to their higher risk for road traffic accidents and assaults. Although many studies did not find a relation between sex and outcome after adjustment for confounding features, a meta-analysis by Farace and Alves found poorer quality of life and worse functional outcomes in women who survived severe TBI compared with men.

The association between ethnic origin and outcome after TBI was controversial until a meta-analysis combining evidence from 5320 patients showed that black patients have a poorer outcome than white or Asian patients. This association has been confirmed by recent studies. The underlying reasons for this association are speculative, but may include differences in genetic constitution, leading to a different response to injury, and differences in access to acute and post-acute care. Identification of such factors is a priority for further research.

Clinical severity
Clinical severity relates to extracranial and intracranial injuries. The overall severity of extracranial injuries is often assessed with the abbreviated injury score or the injury severity score. Most studies on TBI and extracranial injury have included patients with traumatic extracranial injury with or without TBI, and concluded that the coexistence of moderate TBI and extracranial injury is associated with high mortality and morbidity. By contrast, there is no consensus on the prognostic value of major extracranial injury in patients with TBI. Some studies showed that outcome mainly depends on the severity of the primary cerebral damage and is not worsened by the presence of extracranial injuries, but in others, the presence of major extracranial injuries was associated with poorer outcome.

### Table 2: Strength of the association between predictors and outcome (full ordinal GOS) in TBI in the IMPACT database (n=8686)

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)*</th>
<th>Univariate</th>
<th>Multivariate†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age†</td>
<td>2.14 (2.00-2.28)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male§</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>1.01 (0.92-1.11)</td>
<td>0.94 (0.85-1.04)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White§</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>1.30 (1.09-1.56)</td>
<td>1.44 (1.08-1.93)</td>
</tr>
<tr>
<td>Asian</td>
<td>1.09 (0.78-1.52)</td>
<td>1.22 (0.84-1.78)</td>
</tr>
<tr>
<td><strong>Clinical severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>5.30 (3.49-8.04)</td>
<td></td>
</tr>
<tr>
<td>Abnormal extension</td>
<td>7.48 (5.69-9.98)</td>
<td></td>
</tr>
<tr>
<td>Abnormal flexion</td>
<td>3.58 (2.71-4.73)</td>
<td></td>
</tr>
<tr>
<td>Flexion</td>
<td>1.74 (1.44-2.14)</td>
<td></td>
</tr>
<tr>
<td>Localising/obey commands§</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Pupil reactivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both reacting§</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>One reacting</td>
<td>2.70 (2.07-3.53)</td>
<td></td>
</tr>
<tr>
<td>Both non-reacting</td>
<td>4.77 (3.46-6.57)</td>
<td></td>
</tr>
<tr>
<td><strong>Presence of secondary insults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2.67 (2.09-3.41)</td>
<td>2.06 (1.64-2.59)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>2.08 (1.69-2.56)</td>
<td>1.65 (1.27-2.00)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>2.21 (1.56-3.15)</td>
<td>1.63 (1.11-2.40)</td>
</tr>
<tr>
<td><strong>Structural abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>0.45 (0.35-0.67)</td>
<td>0.47 (0.32-0.70)</td>
</tr>
<tr>
<td>Class II§</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Class III/IV</td>
<td>2.62 (2.13-3.21)</td>
<td>2.23 (1.83-2.72)</td>
</tr>
<tr>
<td>Mass lesion on CT</td>
<td>2.18 (1.83-2.61)</td>
<td>1.48 (1.27-1.71)</td>
</tr>
<tr>
<td>Presence of traumatic subarachnoid haemorrhage</td>
<td>2.64 (2.42-2.89)</td>
<td>2.01 (1.83-2.21)</td>
</tr>
<tr>
<td>Presence of epidural haematoma</td>
<td>0.64 (0.56-0.72)</td>
<td>0.63 (0.55-0.72)</td>
</tr>
<tr>
<td><strong>Laboratory variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose‡</td>
<td>1.68 (1.54-1.82)</td>
<td>1.45 (1.36-1.55)</td>
</tr>
<tr>
<td>pH‡</td>
<td>0.80 (0.74-0.88)</td>
<td>0.84 (0.67-0.92)</td>
</tr>
<tr>
<td>Prothrombin time‡</td>
<td>1.41 (1.09-1.99)</td>
<td>1.63 (1.40-1.89)</td>
</tr>
<tr>
<td>Haemoglobin‡</td>
<td>0.69 (0.60-0.78)</td>
<td>0.76 (0.66-0.88)</td>
</tr>
<tr>
<td>Sodium &lt;137 mmol/L¶</td>
<td>1.40 (1.22-1.60)</td>
<td>1.14 (0.91-1.43)</td>
</tr>
</tbody>
</table>

Extracranial injuries were not included in either model. GOS=Glasgow outcome scale. IMPACT=International Mission for Prognosis and Clinical Trial design in TBI. TBI=traumatic brain injury. *From proportional odds analysis. †Adjusted for age, motor score, and pupil reactivity. ‡Odds ratio is for the 75th percentile compared with the 25th percentile. §Reference category. ¶Sodium 137–142 mmol/L used as reference category. Reproduced from Murray et al, with permission from Mary Ann Liebert, Inc.

Figure 2: Prognostic value of different components of traumatic brain injury prognosis (R²) in the IMPACT dataset (n=8686)

The cumulative R² of the full model is 0.35. IMPACT=International Mission for Prognosis and Clinical Trial design in TBI. R²=proportion of variability in outcome explained by the predictor(s). Data from Murray and colleagues.
We recently did a meta-analysis of individual patient data (Maas AIR, unpublished), and found that the conflicting results on the prognostic value of extracranial injuries in previous studies may be explained by an interaction with the severity of brain injury. For patients with more severe brain injuries, the effect of extracranial injury on functional outcome was small, whereas in those with milder brain injuries, extracranial injuries had a more pronounced effect. This suggests that testing for clinically plausible interaction effects is relevant. We also found that extracranial injuries mainly increased the risk of early mortality. Thus, the effect of extracranial injury found in registries that include patients who die early will be larger than the effect found in trials that exclude these patients.

The clinical severity of intracranial injuries is indicated by the level of consciousness, as assessed by the Glasgow coma scale (GCS). Many studies have shown an association between a low score on the GCS and poorer outcome. In patients with more severe injuries, the motor component of the GCS has the greatest predictive value, because eye and verbal response in these patients is often absent. The prognostic value of the eye and verbal components of the GCS become more relevant in patients with less severe injuries who can obey commands. Of note, GCS may fluctuate early after injury, and some patients deteriorate whereas others improve. From a prognostic perspective, assessment of the GCS should therefore be done at a fixed time period, usually on admission after primary respiratory and haemodynamic stabilisation. However, reliable assessment of the GCS may be obscured in the acute setting by medical sedation, paralysis, or intoxication.

Abnormalities in pupillary reactivity indicate brainstem damage or compression and are strongly associated with poorer outcome. Pupillary reactivity is a more stable variable in the early phase after injury than is the GCS, because it is less prone to influences of sedation and paralysis.

Secondary insults
An injured brain is more vulnerable to systemic secondary insults (ie, hypoxia and hypotension) than is a normal, healthy brain. Secondary insults are common after TBI, particularly in the prehospital setting, and can increase the degree of damage. The association of secondary insults with poorer outcome is well established in the prehospital setting or during acute care, and various studies have shown that the combination of hypoxia and hypotension has a greater adverse effect on outcome than can be explained by either insult alone.

Most studies have used a cut-off value for early hypotensive and hypoxic events (eg, any episode with a systolic blood pressure <90 mm Hg). However, detailed analysis of the association between the blood pressure measured on admission and outcome showed that this relation is continuous: low and high blood pressure are both associated with poorer outcome (U-shaped relation). After adjustment for age, motor score, and pupillary reactivity, the effects of higher blood pressure on outcome largely disappear, which suggests that higher blood pressure values are merely indicative of more severe injuries and could possibly be caused by raised intracranial pressure (Cushing response).

Structural abnormalities
The prognostic value of CT characteristics has been well documented, including the status of basal cisterns, midline shift, the presence and type of intracranial lesions, and traumatic subarachnoid haemorrhage. Obliteration of the basal cisterns and the presence of subarachnoid haemorrhage are the strongest CT predictors of outcome. In 1991, Marshall and colleagues introduced a descriptive classification of head injury based on CT characteristics, which focuses on the presence or absence of a mass lesion and differentiates diffuse injuries by signs of increased intracranial pressure (compression of basal cisterns, midline shift). Although the Marshall CT classification has prognostic value, combination of individual CT characteristics in a model, such as in the Rotterdam CT score, provides better discrimination between patients with good versus poor outcomes (tables 3 and 4).

Prognostic studies have mainly focused on CT abnormalities and used relatively broad categorisations. For example, in traumatic subarachnoid haemorrhage (one of the strongest CT predictors of outcome), most studies have concentrated on the presence or absence of this abnormality without differentiating the location (basal cisterns vs cortical) or extent. More detailed analysis and the use of advanced MRI imaging may yield additional prognostic information.

Biomarkers and laboratory variables
Interest in the use of biomarkers, including laboratory variables, has been increasing in recent years. Biomarkers may be used to detect and track pathophysiological phenomena as markers of injury severity, and to help assess prognosis. In mild TBI, a biomarker that could be used to establish the diagnosis or predict the likelihood of secondary damage would...
have great clinical use. In more severe injuries, use of a biomarker to assess injury severity could help to avoid problems with unreliable GCS assessments in patients who are intoxicated or intubated. Several putative serum, CSF, and microdialysate biomarkers have been evaluated in clinical studies of TBI: S100 protein and neuron-specific enolase are among the most widely investigated. Although an association between several biomarkers and outcome has been established, the prognostic value of biomarkers is unclear owing to relatively small numbers analysed in univariate analyses. Biomarker concentrations may correlate with other clinical indicators such as GCS, but they offer limited additional prognostic value over other predictors and need to be assessed in multivariable analysis.

The prognostic value of routinely measured laboratory variables has been more widely investigated. High glucose concentrations, low haemoglobin, low platelets, and coagulation disturbances are the strongest predictors of outcome, and are independently related to poorer outcome. The advantage of laboratory variables is that they are potentially modifiable. The question of causality is relevant when attempts are made to correct abnormal values in the expectation that this will improve outcome. The observed abnormality may simply be an expression or surrogate marker of the severity of injury. Randomised controlled trials are thus required to establish whether the correction of abnormal concentrations is beneficial.

### Clinical course

#### Changes in admission variables

Deterioration in neurological function is a dire prognostic sign that generally indicates progressive brain damage. Early prognosis studies showed that the worst GCS recorded over a given time period is especially predictive of poorer outcome. Deterioration in neurological function has been defined more objectively as neuroworsening (panel), and is highly predictive for poor outcome. In addition to the initial CT scan, follow-up scans also provide prognostic information. A survey among patients with moderate and severe TBI by the European Brain Injury Consortium showed that a substantial proportion of patients with diffuse injury (no mass lesions) on their first CT scan had progressive intracranial damage on subsequent CT examinations. The worst CT scan was more strongly correlated with outcome. Many other studies have confirmed the frequent occurrence of CT progression, but relatively few have addressed the issue of prognostic significance. This is a complex area to study, because CT progression can often lead to therapeutic intervention.

Secondary insults can occur in the clinical setting, despite clinicians’ best attempts to avoid them. Patients are particularly at risk for secondary insults during transport within and between hospitals. The severity, duration, and number of secondary insults contribute to a poorer outcome. The same laboratory variables that have high prognostic value at admission (ie, glucose, platelets, and coagulation disturbances) also have value during the clinical course. Persistently high glucose concentrations are associated with poorer outcomes, even after adjustment for other important predictors. The lowest platelet count during the first 24 h after admission is an independent predictor of outcome after

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**Table 4: Rotterdam prognostic CT score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Basal cisterns</th>
<th>Midline shift</th>
<th>Epidural mass lesion</th>
<th>Intraventricular or traumatic subarachnoid haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cisterns</td>
<td>Normal 0</td>
<td>Compressed 1</td>
<td>Absent 2</td>
<td>Present 0</td>
</tr>
<tr>
<td>Midline shift</td>
<td>No shift or shift ≤5 mm 0</td>
<td>Shift &gt;5 mm 1</td>
<td>Present 0</td>
<td>Absent 1</td>
</tr>
<tr>
<td>Epidural mass lesion</td>
<td>Present 0</td>
<td>Absent 1</td>
<td>Present 1</td>
<td>Sum score +1</td>
</tr>
</tbody>
</table>

**Panel: Criteria for neuroworsening**

- Spontaneous decrease in GCS motor score ≥2 points (compared with previous examination)
- New loss of pupil reactivity
- Development of pupil asymmetry of ≥2 mm
- Other deterioration in neurological status sufficient to warrant immediate medical or surgical intervention

GCS=Glasgow coma scale. Reproduced from Morris and colleagues, with permission from Wolters Kluwer Health.

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Clinical monitoring

In more severely injured patients, invasive and non-invasive monitoring in the intensive-care unit can provide much information. However, approaches to analysis have remained relatively crude. It is difficult to draw clear conclusions on the predictive value of monitored variables because the time of initiation and duration of monitoring vary greatly between and within studies. Summary measures, such as for intracranial pressure monitoring, include the highest, lowest, and mean values overall or per day, and the number of episodes or percentage of time that values are above a predefined threshold. This variability in analysis and reporting confounds comparisons between studies. Furthermore, predictive information on repeated measurements might be better captured in patterns than in single values. Modern statistical approaches are available to analyse repeated measurements per patient, but have seldom been used in TBI studies and hence pose a challenge for future research.

Many studies have confirmed an association of high intracranial pressure, low cerebral perfusion pressure, and decreased brain oxygen tension with poorer outcome. These associations, in combination with our understanding of pathophysiological consequences, form the rationale for guideline recommendations to avoid high intracranial pressure and low cerebral perfusion pressure. Additionally, outcome might be more dependent on intracranial pressure variability and on response to treatment of raised intracranial pressure than on absolute mean values.

Electroencephalography and evoked potentials

Over past decades, there has been interest in electroencephalography (EEG) and evoked potentials or event-related potentials as predictors of outcome. Some have suggested that the predictive ability of EEG is limited because TBI has a greater effect on subcortical axonal fibres than on cortical grey matter, which generates most of the EEG signal. In the post-acute phase, the bispectral index, a measure of level of consciousness by algorithmic analysis of the EEG, has a higher correlation with behaviour than does the EEG and may help in differentiating between a vegetative and minimally conscious state after TBI.

Many studies have shown that somatosensory evoked potentials (SSEPs) are useful predictors of outcome after TBI. Lew and colleagues reported that bilateral absence of cortically recorded median nerve SSEPs within 8 days of severe TBI was strongly predictive of death or persistent vegetative state. A meta-analysis showed that bilaterally negative SSEPs had a 98.5% positive likelihood ratio for an unfavourable outcome. However, the false-positive percentage for bilaterally negative SSEPs may be high in patients with focal lesions, subdural effusions, and after recent decompressive craniectomies. Although results are promising, the evidence on the prognostic effects of these clinical neurophysiological modalities is limited, and the added value over other clinical predictors is uncertain.

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients (n) used in model development</th>
<th>Predictors included (n)</th>
<th>Severity of TBI</th>
<th>Outcome</th>
<th>Risk of overfitting</th>
<th>External validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>600</td>
<td>4</td>
<td>In coma for at least 6 h</td>
<td>GOS at 6 months</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>1980</td>
<td>305</td>
<td>3</td>
<td>In coma for at least 6 h</td>
<td>GOS at 6 months</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>1983</td>
<td>264</td>
<td>4</td>
<td>Severe head injury and GCS motor score ≤5</td>
<td>GOS at 6 months</td>
<td>Intermediate</td>
<td>No</td>
</tr>
<tr>
<td>1984</td>
<td>254</td>
<td>2</td>
<td>GCS ≤8</td>
<td>GOS at 6 months</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>1986</td>
<td>306</td>
<td>3</td>
<td>Severe head injury</td>
<td>GOS at 6 months</td>
<td>Intermediate</td>
<td>No</td>
</tr>
<tr>
<td>1988</td>
<td>523</td>
<td>3</td>
<td>Severe head injury</td>
<td>GOS at 6 months</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>1991</td>
<td>555</td>
<td>4</td>
<td>GCS ≤8</td>
<td>GOS at 12 months</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>1993</td>
<td>315 and 218</td>
<td>5</td>
<td>GCS ≤8</td>
<td>Mortality/GOS</td>
<td>Intermediate</td>
<td>No</td>
</tr>
<tr>
<td>1996</td>
<td>672</td>
<td>3</td>
<td>GCS ≤8</td>
<td>GOS at 6 months</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>1997</td>
<td>380</td>
<td>2</td>
<td>GCS 3–5</td>
<td>GOS at 6 months</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>1997</td>
<td>799</td>
<td>4</td>
<td>GCS ≤8</td>
<td>Mortality at 6 months</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>1999</td>
<td>372</td>
<td>5</td>
<td>GCS ≤12 and GCS &gt;12 if ISS &gt;15</td>
<td>Mortality at 12 months</td>
<td>Intermediate</td>
<td>Yes</td>
</tr>
<tr>
<td>2002</td>
<td>337</td>
<td>3</td>
<td>GCS ≤8</td>
<td>GOS at 6 months</td>
<td>Intermediate</td>
<td>No</td>
</tr>
<tr>
<td>2005</td>
<td>2269</td>
<td>7</td>
<td>GCS ≤12</td>
<td>Mortality/GOS at 6 months</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>2006</td>
<td>304</td>
<td>5</td>
<td>GCS ≤8 and in coma for at least 24 h</td>
<td>GOS(E) at 12 months</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>2008</td>
<td>10 008</td>
<td>4–9</td>
<td>GCS ≤14</td>
<td>Mortality at 14 days/GOS at 6 months</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>2008</td>
<td>8509</td>
<td>3–10</td>
<td>GCS ≤12</td>
<td>Mortality/GOS at 6 months</td>
<td>Low</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ISS=Injury severity scale. GCS=Glasgow coma scale. GOS=Glasgow outcome scale. GOS(E)=GOS (extended). TBI=Traumatic brain injury.

Table 5: Overview of prognostic models in moderate and severe TBI.
Prognostic models

Estimation of prognosis is by definition a multivariable challenge. Predictors should be considered jointly rather than on their own, and can be combined in a multivariable prognostic model to quantify the risk for a particular outcome in individual patients. Combining individual predictors into a model will increase performance and generalisability, and is important because patients could have characteristics that affect the outcome in opposite directions. For example, for a 24-year-old patient with fixed pupils, we would expect a favourable outcome based on age, but an unfavourable outcome based on pupil reactivity.

In our literature search for this Review, we identified 27 prognostic models in 16 studies that met the following criteria: prognostic model for mortality more than 2 weeks after discharge or at 6-month GOS (in English); predictors measured within 24 h after injury; inclusion of more than 200 patients aged older than 14 years; GCS of less than 14 or motor score less than 6; and non-penetrating injury. Many of these models had shortcomings, in particular a high risk of overfitting (eg, predictive performance is much poorer in new patients than expected from the development phase) in ten studies, and lack of external validation (table 5).

The number of predictors considered was usually higher than the number actually included in the final model, and was often too high in relation to the available sample size. As a guide, the maximum number of candidate predictors can be approximated by dividing the number of events (eg, number of patients with poor outcome) by 10 (eg, at most 10 predictors for 100 events). Overfitting is caused by use of statistical techniques for the selection of predictors that are too data-driven, such as backward selection in a small dataset. Overfitting can be assessed by internal validation techniques, such as bootstrap resampling. More important is external validation, such as testing the model’s performance in another setting that differs in time or place. Only five studies reported external validation. These findings are consistent with reviews published by Perel and Mushkudiani and their colleagues.

The models reported by the Corticosteroid Randomisation After Significant Head injury (CRASH) trial investigators and by the IMPACT study group are the most recent, and were developed on the largest numbers of patients (10008 and 8509, respectively). Different sets of prediction models were developed by use of logistic regression analysis and cross-validated on each other. The models are available in score-chart format and in a web-based application. Both studies showed that the largest amount of prognostic information is contained in a core set of three predictors (age, GCS or motor score, and pupillary reactivity; table 6). Development of the CRASH models also included patients with milder injuries, and these models can thus be used to assess such patients. The IMPACT models focused on moderate and severe TBI. Both sets of models can therefore be recommended for prognostic modelling in TBI because they were developed on large numbers of patients and conform to accepted quality criteria for model development, including external validation.

Applications of prognostic models in TBI

Clinical practice

Some estimation of prognosis is consciously or subconsciously used by physicians when informing relatives, making treatment decisions, or allocating resources. Estimates derived from large datasets are preferable to the subjective opinion of a physician, whose experience, no matter how vast, can never match the information contained in data from thousands of patients. 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. Caution is advocated when outcome prediction models are applied in individual patients. Prognostic estimates are only probabilities and cannot provide certainty on an actual outcome.

Research

The main research applications of prognostic models for outcome in TBI include classification and clinical trials. Prognostic risk estimation on hospital admission enables populations to be classified according to their prognostic risk distribution (figure 3). We can therefore use such models to gain insight into differences in the case-mix of different studies. For more on the CRASH and IMPACT models see http://www.crash2.lshtm.ac.uk/ and http://www.tbi-impact.org/
In the design and analysis of randomised controlled trials, prognostic models offer opportunities both in the enrolment and analysis phases. Traditionally, clinical trials use relatively strict enrolment criteria. Some of these criteria are motivated by safety and ethical considerations, but most (eg, age and disease severity) aim to exclude patients with a very good or a very poor prognosis. Patients at these extremes are not likely to benefit from the treatment under investigation. It is statistically more efficient to combine these criteria in a prognostic model.\textsuperscript{111-116} The prognostic estimate can first be used to determine eligibility and then be used for the analysis.

In the analysis phase, prognostic models can adjust for baseline characteristics. This substantially increases statistical power, allows the required sample size to be reduced (by more than 25%).\textsuperscript{117} Prognostic analysis can also make use of the sliding dichotomy, whereby the point of dichotomy of the GOS is differentiated according to the baseline prognostic risk.\textsuperscript{118} For a patient with a very severe injury, survival may be more relevant, whereas for patients with less severe injuries, any outcome worse than good recovery might be considered unfavourable. The sliding dichotomy approach has been adopted for the primary analysis of several phase 3 trials in TBI, stroke, and intracerebral haemorrhage.\textsuperscript{119-121}

However, most prognostic studies in TBI have analysed the GOS by arbitrarily dichotomising it into unfavourable versus favourable outcome groups. Therefore, we cannot assume that predictors that provide good differentiation between death and survival will perform similarly when required to predict good versus poor recovery. To overcome this limitation, a proportional odds model can be used, as was done in the IMPACT studies.\textsuperscript{9} This approach uses the full GOS as outcome instead of a dichotomised GOS, assuming that the predictors differentiate equally well over each possible dichotomisation (proportional odds assumption). A proportional odds model may be more relevant for all patients because it differentiates between death and survival in patients with a poor prognosis, but also between good recovery and anything worse in patients with a good prognosis. Moreover, both the sliding dichotomy and proportional odds models substantially increase statistical power.\textsuperscript{122} The proportional odds assumption may not be valid for all predictors. For example, the presence of severe extracranial injury discriminates between death and survival, but less well between good recovery and moderate disability (van Leeuwen N et al, Erasmus University Medical Centre, Rotterdam, the Netherlands, personal communication).

**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. An example is the standardised mortality ratio (observed deaths/expected deaths, adjusted for baseline characteristics), which is used as a quality score in intensive-care medicine. Expected mortality is commonly derived from severity-of-disease classification systems used in intensive-care units. However, these systems were developed for a general intensive-care population, and their applicability to TBI is uncertain. Prognostic models that are specific to TBI are more useful for setting baselines for clinical audits and benchmarking. These models are of great potential relevance for assessing the quality of health-care delivery, because they have been developed not only for mortality, but also for functional outcome, as assessed by the GOS. Of note, however, the cumulative $R^2$ of the IMPACT model was 0.35, which indicates that 65% of the variation is unexplained, so case-mix adjustment is incomplete.

**Conclusions and future directions**

Prognostic analysis and modelling have great potential in TBI, both for diagnosis and prognosis. Although some of the gaps in our knowledge have been identified, some issues require further investigation. Validated prognostic models have been based mainly on admission characteristics. Although substantial insight has been gained into the prognostic value of variables obtained during the subsequent clinical course, such variables have not yet been widely included in prognostic models. Further research should focus on the quantification of
the additional benefit that might be obtained for outcome prediction. The epidemiology of TBI is changing, and approaches to prehospital care, diagnostic capabilities, and intensive-care monitoring and treatment are continually improving. Consequently, prognostic analysis should be seen as a continuous process that needs updating and validation in contemporary series.123

In the analyses of continuous variables such as age, blood pressure, or laboratory variables, many studies used threshold values, creating a dichotomy or categorisation of continuous predictors (eg, age ≤50 years vs >50 years). Threshold values are increasingly used in clinical medicine in the practice of goal-directed therapy. However, such values are not natural to biological systems, and the collapsing of continuous variables has many disadvantages.124 We recommend that future prediction studies should analyse continuous predictors in a continuous way, possibly even as nonlinear variables.56

A major gap in our knowledge concerns different responses to similar injuries by different individuals. Such differences could in part be genetically determined, and much research will be needed in the areas of genomics and metabolomics to elucidate variability in response. The relevance of genetics may be shown by the observation that recovery is poorer in patients with stroke or TBI who have the APOE ε4 allele than in those who do not have this allele.125 Other genes for which evidence exists for an association with poorer outcome are TP53, COMT, DRD2, and CACNA1A.126 Additionally, response to treatment varies between individuals. Research on factors that predict response to treatment in TBI is underway, including various biomarkers and imaging modalities. Predictive factors may lead to targeted therapies, and take into account individual mechanisms of disease.127 Further research is also needed into more sensitive outcome measures, particularly in milder TBI.

Directly relevant to prognostic research in TBI is better standardisation of data collection and coding to facilitate sharing of results and to allow meta-analysis of individual patient data across studies.128 This will provide the opportunity to improve, validate, and update prognostic models on larger numbers of patients.

The challenge for the immediate future is the implementation of prediction models in clinical practice. The tools are now available in the form of reliable and externally validated models. Clinicians and researchers now need to adopt these models in general clinical and research applications, either to improve quality of care, or to improve the prognostic estimate.

Contributors
HFL and BR contributed equally to this Review, in searching and reading literature, and writing. AIRM provided additional important literature sources and developed the outline. GDS and EWS helped to write the Review.

Conflicts of interest
All authors are members of the IMPACT study group, whose work towards improving the design and analysis of clinical trials in TBI is supported by an NIH grant. EWS, GDM, and AIRM are members of the European Brain Injury Consortium.

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