Determination of Prognosis During Neurointensive Care in Children and Adults with Traumatic Brain Injury: An Update

By Alexis F. Turgeon MD, MSc(Epid), FRCPC, and James S. Hutchison, MD, FRCPC

Several decades of research have advanced our understanding of factors in the prognosis of patients who have suffered a traumatic brain injury (TBI); however, tests or models that demonstrate high levels of accuracy remain elusive. This current issue of Critical Care Rounds presents the currently available early prognostic indicators in children and adults with TBI, and outlines the different scoring systems or models developed in the ICU to determine prognosis after TBI.

Traumatic brain injury (TBI) is a common problem faced by critical care physicians. In Canada, more than 60% of all trauma cases are associated with brain injury and approximately 2500 intensive care unit (ICU) admissions per year are related to severe TBI (Glasgow Coma Scale [GCS] ≤8). It is the most common cause of death and acquired handicaps before the age of 45 in Canada. TBI is most common in young males, but is seen in all ages. Causes of TBI in Canada include motor vehicle collisions, falls, inflicted injuries, and sports-related injuries regardless of the patient’s age. It has also become one of the most common causes of death in nations with emerging economies due to an increase in road traffic accidents.

Despite improvements in the management of patients with TBI over the past few decades, mortality remains high for those with severe injury, ranging from 30%–50% in adults and 10%–30% in children. A significant proportion of survivors will be left with severe neurological disabilities. Severe disability is less common in children and adolescents than adults, and persistent vegetative state is uncommon in pediatric cases. The early determination of a patient’s prognosis is an important concern not only as it relates to mortality, but also for the patient’s global neurological and functional outcome. Indeed, there has been an increased interest in recent years in long-term outcomes. In a recent multicentre cohort study, differences in both mortality and incidence of withdrawal of life-sustaining therapies were observed across Canadian centres in patients with severe TBI. These differences may be explained by variations in the evaluation of the neurological prognosis by medical teams, and by the approach of physicians, families, or communities in terms of the level of care to provide. In a recent survey of Canadian Intensivists, Neurologists, and Neurosurgeons, there was important clinical equipoise observed concerning neuroprognostication among respondents for similar patients with severe TBI.

The identification of evidence-based prognostic tools could help define realistic expectations for physicians and relatives and assist with clinical decision-making. A better understanding of prognosis during the ICU stay would also assist with hypothesis generation about biological mechanisms of injury, risk stratification for quality assurance programs and clinical trials of medical and surgical therapies as well as early rehabilitation strategies.

Outcome Measures

Most clinical predictors and predictive models of prognosis focus on estimates of survival. Considering the important incidence of neurological disabilities following TBI, other outcomes also need to be prioritized to gain a better understanding of the burden of illness. The Glasgow Outcome Scale (GOS) is the evaluation measure most often used to determine outcomes in prospective pediatric and adult studies. It consists of a 5-point scale that includes death, as well as different levels of neurological disability (1=death, 2=vegetative state, 3-severe
neurological disability, 4=moderate neurological disability, and 5=good recovery). An extended version of this tool using an 8-point scale was recently proposed (GOSe) and has recently replaced the standard GOS as an outcome measure in adult studies. In pediatric studies, the 6-point Pediatric Cerebral Performance Category (PCPC) score is also used more frequently. This was developed from the GOS and includes a category for mild disability given the important impact on education and learning during development. More recently, the GOS extended for pediatrics (GOSe Peds) has been recommended by the National Institutes of Health common data elements group as the preferred functional outcome measure for pediatric TBI research. In most studies in both children and adults, the GOS or the GOSe are presented in a dichotomous fashion (ie, an unfavourable prognosis is defined as a GOS score of 1–3, and/or a GOSe of 1–4.)

More detailed outcome measures, including cognitive and neuropsychological tests and quality of life, have not been used to evaluate the ICU population despite their common use for evaluation after rehabilitation. Thus, most prognostic models for outcomes in critically ill traumatic brain-injured patients are designed to determine mortality, GOS, GOSe (in children and adults), and GOSe Peds or PCPC (in children).

Prognostic Indicators

Several independent prognostic indicators for TBI have been identified and relate to preinjury neurological status, etiology of the trauma, clinical signs, neuroimaging, and electrophysiological and biochemical data. In a systematic review of adults with severe TBI, the Brain Trauma Foundation and the American Association of Neurological Surgeons identified 4 significant clinical criteria independently associated with an unfavourable prognosis: the GCS, the patient’s age, pupil diameter and light reflex, and hypotension. Other important prognostic indicators have been identified in previous studies (Table 1).

Clinical Signs and Demographics

GCS

The GCS is a simple, well-established tool for estimating the severity of the brain injury and has a linear relationship with prognosis. The sum score and the motor component subscore are both predictors of mortality and neurological function (GOS score) in children and adults. However, interobserver variability and difference in assessment of the initial GCS can significantly modify the estimation of morbidity and mortality. For example, the mortality associated with a GCS of 3–5 on admission was reported to be 88% when the score was calculated prior to intubation and 66% when a score of 1 was given for the verbal component in intubated adults with TBI. The optimal timing of assessment of the GCS is also debatable, but the consensus is to evaluate it after nonsurgical resuscitation. However, the timing of evaluation is not always reported in studies and often neglected. More importantly, a significant proportion of patients survive with a favourable neurological outcome (GOS 4-5) despite a low GCS score on admission. The GCS therefore, will be useful as a primary risk evaluation but not for accurate prediction of mid or long-term prognosis.

Age

The likelihood of unfavourable neurological outcome is closely associated with the patient’s age. In the case of children, the age thresholds associated with increased risk of mortality or unfavourable functional outcome are below the ages of 3 and 7, respectively. In patients younger than 3 years of age, the risk of death is 30%. For adults, the threshold for increased mortality risk or unfavourable functional outcome is approximately >55–60 years. The risk of death or persistent vegetative state in those above 60 years of age ranges from 75%–90% 3 to 6 months after injury.

Pupillary light reflex and pupil diameter

The bilateral absence of pupillary light reflex on admission – part of the clinical diagnosis of brain death in Canada and several other countries – is correlated with a 70%–95% chance of unfavourable prognosis (GOS 1–2) in adults with severe TBI and with mortality in children with severe TBI. However, up to 5% of these patients still have a positive outlook (GOS 3–5) despite nonreactive pupils after resuscitation. Compared to other features of the neurological examination, pupillary reaction was found to be a robust measurement for prognosis according to a small cohort study even in the presence of medication.

Hypotension

Hypotension in the prehospital setting, in the ICU, or in the operating room is associated with an increased risk of death. A systolic blood pressure (SBP) ≤90 mm Hg is associated with 2-fold and 4-fold increases in adult and child

<table>
<thead>
<tr>
<th>Table 1: Most important early prognostic indicators* of mortality or unfavourable outcome at 6 or 12 months</th>
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<tr>
<td>• Initial post-resuscitation GCS 5</td>
</tr>
<tr>
<td>• Motor score 25,26</td>
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<tr>
<td>• Age 55–60 years 27,28</td>
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<tr>
<td>• Absence of pupillary light reflex 5,25</td>
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<tr>
<td>• Systolic blood pressure ≤90 mm Hg 26,29</td>
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<tr>
<td>• CT scan findings 5</td>
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<tr>
<td>– Intracranial diagnosis 30</td>
</tr>
<tr>
<td>– Presence of subarachnoid hemorrhage 30,31</td>
</tr>
<tr>
<td>– Midline shift ≥5 mm 32</td>
</tr>
<tr>
<td>– Status of basal cisterns 5</td>
</tr>
<tr>
<td>• Mechanism of injury (penetrating &gt; blunt trauma) 28</td>
</tr>
<tr>
<td>• Increased intracranial pressure 33,34</td>
</tr>
<tr>
<td>• Hypoxemia (PaO2 &lt; 60 mm Hg) 29,35</td>
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<td>• Blood glucose level on admission 28,29,36</td>
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</tbody>
</table>

* Admission data or from within the first 24 hours
GCS = Glasgow Coma Scale; CT = computed tomography;
PaO2 = partial pressure of arterial oxygen
mortality with severe TBI, respectively. Hypotension on admission and late hypotension each contributed to a 66% chance of unfavourable neurological outcome (GOS 1–2) compared to 17% in normotensive adults with TBI. One or more episodes of hypotension were also associated with worse neurological outcome in children with TBI. Although the duration of hypotension corresponding to unfavourable outcome is unknown, it should be treated aggressively to prevent secondary brain injury. Current guidelines recommend avoiding SBP ≤90 mm Hg.

Furthermore, high SBP on admission has also been associated with an unfavourable outcome. It is likely an early marker of increased intracranial pressure and thus of the severity of the TBI. As opposed to hypotension, aggressive treatment of high SBP is not a recommended option.

**Hypoxemia**

Low oxygen saturation, mainly during prehospital care, may occur more frequently than initially appreciated in those with severe TBI. Even one hypoxic event of partial pressure of oxygen (PaO₂) <60 mm Hg (adjusted odds ratio 1.65; [1.37–2.00]) has been noted to increase mortality. Current recommendations are to avoid any episodes of oxygen saturation <90% or PaO₂ <60 mm Hg.

**Intracranial pressure (ICP) and cerebral perfusion pressure (CPP)**

Increased ICP and low CPP are associated with unfavourable outcomes in severe TBI in both children and adults. In one study of continuous CPP monitoring, the combination of duration and amplitude of low CPP was highly predictive of outcomes of TBI. The treatment of increased ICP and low CPP has been the key feature of the management of patients with severe TBI.

**Radiological Imaging**

**Computed tomography (CT) scan**

The etiology, localization, and extent of the lesion on CT imaging provide important prognostic information in adults. Four important predictors were closely linked with prognosis in the review of the American Association of Neurological Surgeons: the absence of basal cisterns, presence of subarachnoid hemorrhage, presence of a midline shift, and the type of lesion. The absence of basal cisterns had a positive predictive value of 73%–87% for unfavourable outcomes at 6 and 12 months, while the presence of a subarachnoid hemorrhage doubled the mortality. In a large prospective cohort study, a midline shift >5 mm in patients ≥45 years of age was associated with a positive predictive value for unfavourable outcome (GOS 1–2) of 78%, and the positive predictive value was 79% for a lesion with a volume >15 mL. The same lesions observed on the CT scan are also associated with unfavourable prognoses in children with TBI. Different scoring systems were also proposed for risk stratification in adult patients. The most frequently used classification was created by Marshall and colleagues (Marshall score). This was based on the Traumatic Coma Data Bank and originally developed to determine prognosis at hospital discharge. The classification has a strong correlation with the GOS at discharge. The Marshall score is not validated for use in children.

The recent technology of CT perfusion has been available in many centers. This technology estimates the quantity of blood flowing to specific areas of the brain, allowing extrapolation for determining underperfused and oligemic areas. Its potential and properties as a future prognostic tool require further study.

**Magnetic resonance imaging (MRI)**

In adults, the sensitivity of the MRI is generally better than CT at detecting structural damage. Conventional MRI provides useful information on vascular and axonal damage while diffusion MRI allows a better appreciation of secondary lesions such as edema. Detailed imaging techniques are vital since the location of an injury is also prognostic. In a prospective study of 57 patients, lesions of the corpus callosum, the basal ganglia, and the midbrain were closely associated with unfavourable outcome (GOS 1–3). In children and adults with severe TBI, bilateral brainstem injury had positive and negative predictive values of 0.86 and 0.88, respectively, for unfavourable outcome at 12 months post-injury.

Newer MRI techniques, including diffusion-tension imaging (DTI), susceptibility-weighted imaging (SWI), and functional MRI (fMRI), suggest enhanced detection of microhemorrhages and subtle axonal injuries. However, although these new techniques are promising for prognostic assessment, very few studies have been conducted linking these findings to outcome and routine recommendations for its use cannot be made.

**Nuclear Medicine**

**Single-photon emission CT (SPECT) and positron emission tomography (PET)**

Newer nuclear medicine imaging technologies have shown promise in their abilities to correlate findings to long-term prognosis. Among these, SPECT and PET are used to assess regional brain metabolism. However, as with other new technologies, they require further evaluation prior to gaining acceptance as routine prognostic indicators.

**Electrophysiological Tests**

**Somatosensory evoked potential (SSEP) and brainstem auditory evoked potential (BAEP)**

In systematic reviews evaluating the use of SSEP in adults and children with TBI, a bilateral absence of potentials at the median nerve was associated with a 95% positive predictive value of unfavourable neurological prognosis at 3–12 months (GOS 1–2). All SSEPs were performed within the first 2 weeks in the ICU. These findings were consistent with a previous systematic review. However, unilateral absence or abnormal evoked potentials were difficult to interpret since most of these patients experienced awakening from coma (GOS 3–5). In a recent study by Houlden and colleagues, a scoring system that proposed different combinations of normal, abnormal or absent SSEP unilaterally or bilaterally showed promising prog-
nostic value. SSEP has the highest specificity for unfavourable prognosis after TBI and should be used in clinical practice.

BAEPs were evaluated in small cohort studies early after experiencing TBI. In pooled results from 7 studies (N=389), all but 1 patient showing unilateral or bilateral absence of BAEP experienced a suboptimal outcome (GOS 1–2) at 3–12 months.90 BAEPs are not used often in clinical practice.

**Electroencephalography (EEG)**

Many studies have evaluated the prognostic value of EEG for long-term outcome in TBI. With the advent of more affordable and user-friendly technology, the use of EEG is expanding in the ICU. Continuous EEG monitoring is more often used to diagnose seizures and/or monitor treatment. Although the technology is used extensively by neurologists, the information provided by an isolated EEG is unlikely to provide relevant long-term prognostic information. Beyond isoelectric patterns which are clearly associated with an unfavourable outcome, the absence of EEG reactivity has a positive predictive value of 93% for an unfavourable outcome (GOS 1–3).82,83 Additionally, lack of alpha variability, representative of thalamic damage, is associated with unfavourable prognosis at 6 months.84 As opposed to SSEP, sedation produces some variation in EEG evaluation. The advent of variability analysis and more recently of synchronicity has brought a renewed interest in the prognostic value of the EEG.85,94 However, considering the complexity of data interpretation for assessing EEG reactivity and synchrony, these EEG patterns are not yet used in clinical practice.

**Biomarkers**

Biomarkers from blood, spinal fluid, or from brain microdialysis are emerging prognostic tools. Serum biomarkers such as S-100B protein, neuron-specific enolase, glial fibrillary acidic protein, and interleukin-8 were correlated with unfavourable outcome at 12 months in both children and adults with TBI (GOS 1–3 and PCPC 4–6).85,87,90 Protein S-100B is the most studied biomarker in neurocritical care populations. Changes in the expression of this protein are associated with the severity of brain damage and survival.91 Combining brain-specific biomarkers with inflammatory proteins improves the prognostic accuracy of serum biomarkers in TBI.92 Mass spectrometry has recently been used for the discovery of novel brain-specific prognostic biomarkers in TBI.93 A lactate/pyruvate ratio >25 obtained from brain dialysis was found to correlate with unfavourable outcome (GOS 1–3) at 6 months.94 Brain glucose level, glyceral, and glutamate might also be associated with prognosis as much as brain pH.95,96 Clinical research on biomarkers is growing and their use as a prognostic determination tool is promising.

**Predictive Models**

Over the last decades, severity-of-illness models to predict mortality or morbidity in the ICU were developed in the absence of clinically significant accuracy from sole predictors. Having been developed in a general ICU population or in a specific TBI population, these models are labeled as generic or specific.

**Generic models**

Generic models were developed for risk stratification, outcome research and quality assurance. However, the Acute Physiology And Chronic Health Evaluation (APACHE) scoring,97-99 the Simplified Acute Physiology Score (SAPS),100,101 and the Mortality Probability Model (MPM)102,103 were validated in the adult TBI population as prognostic tools.104-106 The 3 main generic models – the APACHE II score, the SAPS II score and the MPM II (admission and 24 hours) to the GCS score – were compared using a subgroup of adult patients with head injury (n=401) from a large, multicentre cohort study.106 All models predicted mortality at hospital discharge with good discrimination (area under the receiver operating characteristic curve >0.9). Albeit, both the SAPS II and APACHE II slightly underestimated mortality compared to the MPM II. In a single-centre study of 200 patients, the APACHE III score was found to be superior to the APACHE II and the GCS in prediction of hospital mortality, with a sensitivity of 87% specificity of 81%.107 The Index of Independence in Activities of Daily Living (Index of ADL), classifying functional outcomes in 7 grades, was also assessed as a long-term outcome. Again, the APACHE III score provided the better estimate with a sensitivity of 73% and a specificity of 82% for unfavourable functional status measured by the Index of ADL (score of ≤4). Correlation with other long-term functional outcomes, such as the GOS at 1 year, was only validated in a small, retrospective cohort study with 70 patients.108

To specifically address the broader trauma population, other generic models were developed. The Abbreviated Injury Scale (AIS), the Injury Severity Score (ISS), the Revised Trauma Score (RTS) and the Trauma Injury Severity Score (TRISS) are the most often used scoring systems for estimating mortality in this population.108-112 Using a large cohort from an American trauma registry (≥7700 patients) with different degrees of head injury severity, the Head component of the AIS (score from 1–6; 6 = fatal injury) predicted hospital mortality in all cases (23/23) when the score was 6.24 However, the maximum score of 6 is infrequent and might predict hospital deaths that would be obvious without the help of a scoring system. A Head AIS of 5 also predicted hospital mortality, albeit with a low positive predictive value of 65%. Overall, the prognostic value of the Head AIS was not significantly better than the GCS. In a previous cohort study of 109 patients, values from 0–3 of the Head AIS had shown a positive predictive value of 95% for favourable outcomes at 6 months (GOS 4–5).113

In a large retrospective cohort study, the APACHE III score was observed to be more sensitive and specific than the APACHE II, the TRISS and the 24-hour ICU point system (based on the GCS, the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen [PaO₂/Fio₂]), and the fluid balance within the first 24 hours after injury114 to estimate hospital mortality in a subgroup of patients with TBI.115 The performance was globally better
in nonoperative head injury. In a small cohort study from a different American trauma registry, the Head AIS was not shown to be a significant predictor at 1 year for 2 measures of function and independence: the Disability Rating Scale and the Community Integration Questionnaire (CIQ).\textsuperscript{116-118} In the same study, the RTS – a score combining the GCS with the heart and respiratory rates – did show a significant correlation with these functional long-term outcomes when associated with other demographic variables.\textsuperscript{118}

Recently, the accuracy of the Pediatric Index of Mortality (PIM) was evaluated in 2575 children with head injury admitted to pediatric ICUs in England and Wales.\textsuperscript{8} Overall, the model performed well; however, mortality was lowest in the mid-volume units. The Pediatric Risk of Mortality (PRISM) Score and the Pediatric Trauma Score (PTS) have also been examined in children with TBI. A PRISM II score >17.5 had a sensitivity of 80% and a specificity of 88% in predicting mortality in nonaccidental TBI in children.\textsuperscript{119} In another study, using multivariate analysis in 222 children with severe TBI, both PRISM II >20 and bilateral mydriasis were associated with unfavourable outcome.\textsuperscript{4}

Thus, generic models are well correlated with short-term outcomes such as hospital mortality, but very few studies attempted to validate these models for long-term functional outcomes. Moreover, none of these models has a sufficiently high positive predictive value to be used outside of risk stratification and quality assurance.

Specific models

Most prognostic models for patients with severe TBI were developed in an attempt to estimate the occurrence of unfavourable neurological prognosis using different outcomes. These so-called prediction rules are normally developed to determine the probability of a specific outcome and then help physicians interpret clinical information.\textsuperscript{120} However, depending of the outcome of interest and further decisions associated with this outcome, the prediction rule has to be very sensitive or very specific. Many specific models using different statistical methodologies were developed over the years with variable success (Table 2).\textsuperscript{25,26,46,121-123}

The first prediction rule to have been developed was the GCS. This score has been so well implemented in clinical practice as part of the standard clinical examination that we tend to forget it is a specific prediction model developed in the TBI population.\textsuperscript{1} Considering the limitations of the GCS previously discussed, other models were proposed for predicting short-, mid-, and long-term outcomes of mortality or neurological functions.

The first prediction trees for severe head injury were proposed 20 years ago using clinical and demographic variables of 555 patients on admission (pupillary response, age, motor response, and intracerebral lesions) to predict the GOS at 12 months.\textsuperscript{25} The predictive accuracy of the model was greater for good recovery (GOS 4–5) or death (GOS 1), with a positive predictive value of 82%, than for intermediate neurological outcomes. In another study, 5 admission variables – age, GCS, ISS, pupillary reactivity, and hematoma on CT scan – were used to derive a prediction rule that showed 85% accuracy to predict mortality at 1 year after moderate and severe TBI.\textsuperscript{46} The rule was derived from a prospective cohort of 372 patients and validated in a subsequent cohort of 520 patients from the same centre. Using data from a large epidemiologic study performed in Taiwan, Hsu and colleagues\textsuperscript{124} derived and validated a rule to estimate the GOS assessed within 12 months after injury. This neural network model was developed using 10 admission variables and obtained a global accuracy of 75.8% to predict the GOS. Despite a good specificity for worst outcomes on the GOS, this accuracy is lower than the one observed in previous studies. As well as for the 3 rules previously described, most specific models were developed using nonmodifiable variables. However, 2 prognostic studies included potentially modifiable variables to generate their prediction rules.\textsuperscript{25,125} Hukkelhoven and colleagues used data from 2 multicentre clinical trials\textsuperscript{26,35} previously performed in Europe and North America. Among 7 predictive admission characteristics, hypoxia and hypotension were included along with age, motor score, pupillary reactivity, CT scan classification, and presence of subarachnoid hemorrhage. This rule, developed to determine mortality and unfavourable outcomes (GOS 1–3) at 6 months, showed accuracy advantageously comparable to the rules previously cited. The use of potentially modifiable predictors such as hypoxia and hypotension means inclusion of secondary brain injury components. In a small prospective study (N=124) conducted by Andrews and colleagues,\textsuperscript{122} the influence of variables leading to secondary brain injury to determine functional outcomes (GOS) at 12 months was evaluated. In that study, 3 main prediction trees were created: one using only demographic data, a second one using only injury data and a last combining both types of variables. The tests accuracy ranged from 61%–64% in the validation phase. A longer duration of insult correlated with unfavourable GOS for most of the injury data.

In a recent study of 315 children with TBI,\textsuperscript{126} it was observed that age <2 years, GCS ≤5, accidental hypothermia, hyperglycemia, and coagulopathy on admission were significantly associated with mortality using a logistic regression analysis. These variables were used to develop a prediction score ranging from 0–6 for mortality. A score of 0 was associated with 100% mortality. A recent small study (N=28) in children showed that combining postresuscitation GCS scores with a day-1 serum biomarker (interleukin-8) level produced a sensitivity of 100% and a specificity of 96% for prediction of unfavourable outcome (GOS 1–2).\textsuperscript{127} These studies need to be validated in large prospective cohorts of pediatric patients.

More recently, 2 prognostic models using large datasets from previous prospective studies in adults were developed.\textsuperscript{124,125} Using admission data from a large-scale, randomized, controlled trial on steroids in moderate and severe TBI (N=10 008 patients), the Medical Research Council (MRC) CRASH Trial Collaborators\textsuperscript{124} developed 4 prognostic models using age, GCS, pupillary reactivity, presence or absence of major extracranial injury and select findings on CT scan (when available) with 14-day mortality and the 6-month GOS (best area under the curve [AUC]: 0.88). These prognostic models at 6 months were externally validated using a large dataset from the Interna-
<table>
<thead>
<tr>
<th>Author, period of data collection</th>
<th>No. of patients</th>
<th>Data</th>
<th>Patient selection</th>
<th>Outcome</th>
<th>Predictors</th>
<th>Model</th>
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<th>Performance</th>
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<tr>
<td>Choi et al, 1976-1989</td>
<td>555</td>
<td>Retrospective, single centre</td>
<td>GCS &lt; 9</td>
<td>GOS at 1 year</td>
<td>4 admission variables: age, pupillary reactivity, motor response, intracerebral lesion</td>
<td>Tree model</td>
<td>Limited</td>
<td>Accuracy: 78% (60-82%)</td>
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<td>Signorini et al, 1989-1991</td>
<td>372</td>
<td>Prospective, single centre</td>
<td>GCS ≤ 12 or &gt; 12 with ISS &gt; 16</td>
<td>Mortality at 1 year</td>
<td>5 admission variables: age, GCS, ISS, pupillary reactivity, hematoma on CT</td>
<td>Logistic regression</td>
<td>Limited</td>
<td>Accuracy: 85%</td>
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<td>Hsu et al, 1995-1998</td>
<td>3345</td>
<td>Database, multicentre</td>
<td>GCS ≤ 12</td>
<td>GOS in first 12 months</td>
<td>10 variables: age, number of nonreactive pupils, motor response, verbal response, eye opening, use of helmet, hematoma on CT, subdural hematoma on CT, craniotomy, alcohol-related</td>
<td>Neural network</td>
<td>Yes</td>
<td>Accuracy: 76% Sensitivity: 48%–92% Specificity: 89%–99% (depending on the GOS score)</td>
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<tr>
<td>Andrews et al, 1989-1991</td>
<td>124</td>
<td>Prospective, single centre</td>
<td>GCS ≤ 12 or &gt; 12 with ISS &gt; 15</td>
<td>GOS at 12 months</td>
<td>4 variables (time not reported): age, GCS, type of accident, referral, isolated head injury, CPP, hypotension, hypocarbia, sex, type of hematoma, evacuation of hematoma</td>
<td>Tree model</td>
<td>No</td>
<td>Accuracy: 60%–64%</td>
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<tr>
<td>Rovlias et al, 1993-2000</td>
<td>345</td>
<td>Prospective, single centre</td>
<td>GCS &lt; 9</td>
<td>GOS at 6 months</td>
<td>6 variables (time not reported): age, GCS, pupillary response, Intracranial diagnosis, glucose level on Day 2, SAH, WBC on admission)</td>
<td>Tree model</td>
<td>No</td>
<td>Accuracy: 87% PPV for unfavourable outcome: 85%</td>
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<tr>
<td>Hukkelhoven et al, 1991-1994</td>
<td>2269</td>
<td>2 RCTs, multicentre</td>
<td>GCS ≤ 12</td>
<td>GOS at 6 months</td>
<td>7 admission variables: age, gender, cause of injury, motor score, pupillary reactivity, hypopxia, CT classification, SAH</td>
<td>Logistic regression</td>
<td>Yes</td>
<td>AUC*: 0.83–0.89</td>
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<td>Combes et al, 1989-1992</td>
<td>132</td>
<td>Prospective, single centre</td>
<td>GCS &lt; 9</td>
<td>GOS (unclear time period)</td>
<td>3 admission variables: age, motor response, hypoxia</td>
<td>Logistic regression</td>
<td>No</td>
<td>Accuracy: 73% Sensitivity: 93% Specificity: 57%</td>
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<tr>
<td>Perel et al (MRC CRASH database), 1999-2004</td>
<td>10 008</td>
<td>Prospective multicentre</td>
<td>GCS ≤ 14</td>
<td>GOS at 6 months, 14-day mortality</td>
<td>7 admission variables: age, GCS, pupillary reactivity, major extracranial injury, petechial hemorrhages, obliteration of third ventricle, SAH, midline shift, nonevacuated hematoma</td>
<td>Logistic regression</td>
<td>Yes</td>
<td>AUC: 0.83–0.88</td>
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<td>Steyerberg et al (IMPACT database), 1984-1997</td>
<td>8509</td>
<td>Prospective multicentre</td>
<td>GCS ≤ 12</td>
<td>GOS at 6 months, mortality</td>
<td>10 admission variables: age, GCS motor score, pupillary reactivity, hypoxia, hypotension, Marshall score, SAH, epidural hematoma, blood sugar, hemoglobin level</td>
<td>Logistic regression</td>
<td>Yes</td>
<td>AUC: 0.78–0.80</td>
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</table>

GOS = Glasgow Outcome Scale; ISS = Injury Severity Score; CPP = cerebral perfusion pressure; SAH = subarachnoid hemorrhage; WBC = white blood cell count; PPV = positive pressure ventilation; RCT = randomized, controlled trial; AUC = area under the curve; MRC = Medical Research Council; IMPACT = International Mission for Prognosis And Clinical Trial

* Area under the operating curve in the validation dataset.
Models have been developed to improve this level of favourable versus unfavourable outcome. Many prognostic models were developed using the following admission data from 8509 patients: age, GCS motor score, pupillary reactivity, hypoxia, hypotension, Marshall score, and select CT scan features to predict mortality and the GOS at 6 months. These models proposing a scoring system were externally validated using the MRC CRASH dataset (best AUC 0.80). The prognostic models developed using the MRC CRASH and the IMPACT databases are the largest and the most accurate using admission data to date.

Limitations
A number of limitations to these prognostic models must be considered. First, many models predate advances in CT scan as part of bedside care, monitoring, and consensus recommendations for TBI management. Additionally very few models accounted for secondary cerebral injuries, which are not always avoidable despite the application of appropriate prevention measures. Most prognostic models use admission variables which could be premature to show high accuracy. Other prognostic models used complex formulas requiring computer software assistance making their utilization less convenient in clinical practice. More importantly, many models were derived from single centres, small cohorts, retrospective data, or were never externally validated in a distinct dataset, thus precluding generalizability of the findings.

Conclusion
Over the past decades, there has been an important interest in the understanding of prognosis in critically ill patients with TBI. Yet, long-term neurological outcomes are challenging to determine early after the event despite the identification of many prognostic indicators. There are several promising innovative technologies, but none are yet appropriate for use in current clinical practice. There is no current prognostic test that is able to reliably delineate favourable versus unfavourable outcome. Many prognostic models have been developed to improve this level of uncertainty and address these limitations. However, no model is sufficiently precise to be standard of care for prognostic evaluation of an adult TBI population. Furthermore, few models have been developed and validated for the pediatric population.

Considering that most deaths in critically patients with TBI occur following the withdrawal of life-sustaining therapies, more precise prognostic instruments with long-term neurological functional outcome measures in both children and adults are urgently required. These instruments could not only provide better evidence-based expectations for physicians, family and relatives, but also a better risk stratification of patients with TBI for evaluating system performance and standardize future research.

References

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predicting survival and mortality of ICU patients using objectively derived mortality probability models (MPM II) based on an international cohort of systemic severe brain-injured patients.