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Early Determination of Prognosis in Traumatic Brain Injury: Beyond the Glasgow Coma Scale

BY ALEXIS TURGEON, MD, MSc, FRCPC

Traumatic brain injury (TBI) is a common problem faced by intensivists. In Canada, >60% of all trauma cases are associated with brain injury and, every year, approximately 2500 of intensive care unit (ICU) admissions are related to severe TBI (ie, Glasgow Coma Scale [GCS] <9).¹⁻³ Over the last few decades, management of patients with TBI has improved with the development of guidelines to standardize patient care and the establishment of specialized neurocritical care units.^{4,5} However, mortality remains high, ranging from 30% to 50%. For patients who survive, a significant proportion will suffer from severe neurological disabilities.⁶⁻⁸ The early determination of a patient's prognosis is an important concern, not only because it relates to mortality, but also to the patient's global neurological and, ultimately, functional outcome. Until recently, the outcomes of critical illness were only considered within the ICU; however, there has been increasing interest in long-term outcomes following a period of rehabilitation.⁹ Evidence-based prognostic tools could help define realistic expectations for physicians and relatives and support clinical decision-making. A better understanding of prognosis would also assist with hypothesis generation about biological mechanisms that, in turn, could aid research and the risk stratification of patients for quality assurance programs/research. Over the years, many predictors of prognosis have been identified and several models have been proposed to estimate mortality and neurological prognosis post-TBI at different time-periods. This issue of *Critical Care Rounds* reviews the most important early factors associated with prognosis in the TBI adult population and the different scoring systems or models that have been developed in the ICU to determine prognosis after TBI.

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 outcome measures need to be taken into account to gain a better understanding of the burden of illness. The most frequently used outcome measure in predictive studies is the Glasgow Outcome Scale (GOS), a 5-point scale that considers 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).¹⁰ An extended version, based on 8 points, was also recently proposed (GOS-e) and is slowly replacing the standard GOS as an outcome measure.¹¹ Other more precise outcome measures, involving neuropsychological tests, cognitive tests, tests of functional measures or quality of life, have not been used extensively in studies performed in the ICU population, despite being commonly used to evaluate the rehabilitation population. Thus, most predictive factors and models of prognosis in the ICU population were solely identified or established to determine mortality or neurological prognosis using the GOS at different time periods after the trauma.

Predictive factors

Several independent predictive factors of prognosis in the TBI population have been identified over the years. These predictors are related to the etiology of the trauma, clinical signs, neuro-imaging, and electrophysiological and biochemical data. In a systematic review, the Brain Trauma Foundation and the American Association of Neurological Surgeons identified 4 significant clinical criteria that are independently associated with poor prognosis: the GCS, the patient's age, pupil diameter and light reflex, and hypotension.⁴ Other important predictors, not



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Correspondence:
John Granton, MD
The Toronto General Hospital
11 NCSB, Rm. 1170
585 University Avenue
Toronto, ON, M5G 2N2
Fax: 416-340-3359

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Table 1: The most important early predictors of mortality or unfavourable outcome (Glasgow Outcome Scale [GOS] 1-3) at 6 or 12 months

Predictors*

- Initial post-resuscitation GCS⁴
- Motor score^{12,13}
- Age ≥ 55 or ≥ 60 years^{14,15}
- Absence of pupillary light reflex^{4,12}
- Systolic blood pressure ≤ 90 mm Hg^{13,16}
- CT scan findings⁴
 - intracranial diagnosis¹⁷
 - presence of subarachnoid hemorrhage^{17,18}
 - midline shift ≥ 5 mm on CT scan¹⁹
 - status of basal cisterns⁴
- Mechanism of injury (penetrating > blunt trauma)¹⁵
- Increased intracranial pressure^{20,21}
- Hypoxemia (PaO₂ <60 mmHg)^{16,22}
- Glucose level on admission^{15,23}

GCS = Glasgow Coma Scale

* Admission data or from within the first 24 hours

discussed below, were also identified in previous studies (Table 1).

Clinical signs

GCS: The GCS is a simple and established tool for estimating the severity of a head injury and has a linear relationship with prognosis.¹ The sum score and the motor component sub-score are both predictors of mortality and neurological function (GOS score).²⁴ However, inter-observer variability and differences in assessment of the initial GCS can significantly modify the estimation of morbidity and mortality.²⁵ For example, mortality associated with a GCS of 3 to 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 patients.^{4,26} The timing of assessment of the GCS is also debatable, but the consensus is to evaluate it after nonsurgical resuscitation.²⁷ More importantly, a significant proportion of these patients survive and have a good neurological prognosis (GOS 4-5), despite a low GCS score. The GCS, therefore, may be useful for a primary risk evaluation, but not for accurate mid- or long-term prognosis.

Age: The probability of poor outcome increases in a step-wise manner with patient age.¹⁴ Many authors have suggested a threshold, from which the association with a poor neurological prognosis is prominent.²⁸⁻³⁰ The most commonly accepted thresholds are between age 55 and 60 years, which correlates with a mortality risk or poor neurological prognosis (GOS 1 or 2) of 75% to 90% at 3 or 6 months.

Pupillary light reflex and pupil diameter: As part of the clinical diagnosis of brain death in Canada and in many other countries, the absence of pupillary light reflex is obviously correlated with a >70% to 95% chance of poor prognosis (GOS 1 or 2) in the TBI population.⁴ However, up to 5% of these patients may still have a good prognosis (GOS 3, 4, or 5) despite unreactive pupils post-resuscitation.³¹ Compared to other features of the neurological exam, pupillary reaction was found to be relatively stable with respect to medication in a small cohort study.³²

Hypotension: Hypotension on admission is clearly associated with an increased mortality. A systolic blood pressure ≤ 90 mm Hg is associated with a 2-fold increase in mortality risk compared to normal blood pressure.¹⁶ Chestnut and colleagues also observed that both hypotension on admission and late hypotension were associated with a 66% chance of poor neurological outcome (GOS 1 or 2) compared to 17% in normotensive patients. Hypotension is, therefore, a potentially modifiable predictor of prognosis, thus introducing the concept of prevention of secondary brain injury.

Diagnostic tests

Computed tomography (CT) scan: The etiology, localization, and extent of the lesion obtained from a CT scan provide important prognostic information. Four important predictors were closely linked with prognosis in a review from the American Association of Neurological Surgeons: the absence of basal cistern, presence of subarachnoid hemorrhage, presence of a midline shift, and the type of the lesion.⁴ The absence of basal cisterns had a positive predictive value of 73% to 87% for unfavourable outcomes at 6 and 12 months,³³⁻³⁵ while the presence of a subarachnoid hemorrhage doubled the mortality.^{17,18} In a large prospective cohort study, a midline shift >5 mm in patients aged ≥ 45 years was associated with a positive predictive value for poor outcome (GOS 1-2) of 78%.¹⁹ In the same study, a lesion with a volume >15 mL had a positive predictive value for poor outcome (GOS 1-2) of 79%. Different scoring systems have also been proposed for risk stratification of patients.^{21,36-38} The most common is the classification created by Marshall et al, based on the Traumatic Coma Data Bank, and originally developed to determine prognosis at hospital discharge.³⁸ This classification has a strong correlation with the GOS at discharge.

Magnetic resonance imaging (MRI): The sensitivity of MRI is generally better than CT in detecting structural damage.³⁹ Conventional MRI provides useful information on vascular and axonal damages, while diffusion MRI allows a better appreciation of secondary lesions such as edema.⁴⁰ In a prospective study of 57 patients, lesions of the corpus callosum, the basal ganglia, and the midbrain were closely associated with an unfavourable outcome (GOS 1-3).⁴¹ However, the relationship between MRI and long-term outcome has not been extensively evaluated in the absence of a classification of the structural damages.

Single photon emission tomography (SPECT) and positron emission tomography (PET): Newer diagnostic imaging tests have shown some promising abilities to predict long-term prognosis, but further evaluations are required prior to using them as prognostic indicators in a clinical setting.^{39,42}

Somatosensory evoked potentials (SSEP), brain stem auditory evoked potentials (BAEP), and electroencephalography (EEG): In a recent systematic review of the use of SSEP, a bilateral absence of potentials at the median nerve was associated with a 95% positive predictive value of poor neurological prognosis at 3 to 12 months (GOS 1 or 2).⁴³ All SSEPs were performed within the first 2 weeks in the ICU. Findings were consistent with a previous systematic review;⁴⁴ however, unilateral absence or abnormal evoked potentials were difficult to interpret since most of the patients experienced awakening from coma (GOS 3, 4 or 5). Despite

having the highest specificity for poor prognosis, SSEPs are not often used in clinical practice. BAEPs have been evaluated in small cohort studies early after TBI. In pooled results from 7 studies (n = 389), all patients exhibiting uni- or bilateral absence of BAEP (except for 1 patient) had an unfavourable outcome (GOS 1-2) at 3 to 12 months.⁴⁴ Many studies have evaluated the prognostic value of EEG for long-term outcome in TBI. Beyond isoelectric patterns clearly associated with brain death, in the absence of confounding factors, the absence of EEG reactivity has a positive predictive value of 93% for an unfavourable outcome (GOS 1-3).^{45,46} Considering the need for expert data interpretation and the difficulty in continuous recording of data, this technical tool has been used less often over the past few years for prognostic determination outside of brain death.

Biomarkers

Biomarkers from blood, spinal fluid, or brain microdialysis are emerging as potential prognostic tools. Many serum markers (eg, S-100B protein, neuron-specific enolase, interleukin-8) have correlated with an unfavourable outcome at 12 months (GOS 1-3).⁴⁶⁻⁴⁹ A lactate/pyruvate ratio >25 obtained from brain dialysis correlated with an unfavourable outcome at 6 months (GOS 1-3).⁵⁰ Brain glucose level, glycerol, and glutamate may also be associated with prognosis as much as brain pH.^{51,52} The use of biomarkers is promising and they may become a part of prognostic determination tools in the upcoming years.

Predictive models

Over the last 20 years, 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 described as “generic” or “specific,” respectively.

Generic models: These were developed for the purpose of risk stratification, outcome research, and quality assurance. However, the Acute Physiology And Chronic Health Evaluation (APACHE) scoring,⁵³⁻⁵⁵ the Simplified Acute Physiology Score (SAPS),^{56,57} and the Mortality Probability Model (MPM)^{58,59} have been validated in the TBI population as clinical prognostic tools.⁶⁰⁻⁶² Using the subgroup of adult patients with head injury from a large multicentre cohort study, Alvarez et al compared 3 main generic models, the APACHE II score, the SAPS II score, and the MPM II (admission and 24 hours) to the GCS score.⁶² In this prospective cohort of 400 patients from Europe and North America, all 4 models predicted mortality at hospital discharge with good discrimination (ROC >0.9), but SAPS II and APACHE II both 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 GCS in predicting hospital mortality, with a sensitivity of 87% and a specificity of 81%.⁶³ 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 (mean follow-up of 2.2 years). Again, the APACHE III score had the better estimate, with a sensitivity of 73% and a specificity of 82%

for poor functional status as 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 of 70 patients.⁶¹

In order to specifically address the broader trauma population, other generic models were developed during the same period. 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.⁶⁴⁻⁶⁸ Using a large cohort from an American trauma registry of >7700 patients with different degrees of head injury severity, Demetriades and colleagues observed that the “head” component of the AIS (score from “1” [minor] to “6” [fatal injury]) predicted hospital mortality in all cases (23/23) when the score was 6.¹⁵ However, the maximum score of “6” is infrequent and may predict hospital deaths that would be obvious without the help of a scoring system. A Head AIS of “5” also predicts hospital mortality, but 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” to “3” of the head AIS had a positive predictive value of 95% for good outcomes at 6 months (GOS 4-5).⁶⁹

In a large retrospective cohort study, Vassar et al observed that the APACHE III score was more sensitive and specific than the APACHE II, the TRISS, and the 24-hour ICU point system (based on the GCS, the PaO₂/FiO₂ ratio, and the fluid balance within the first 24 hours after injury)⁷⁰ to estimate hospital mortality in a sub-group of patients with TBI.⁷¹ 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 or the Community Integration Questionnaire (CIQ).⁷²⁻⁷⁴ In the same study, the RTS, a score combining the GCS and the heart and respiratory rate, revealed a significant correlation with these functional long-term outcomes when associated with other demographic variables.⁷⁴

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

Specific models: Most of the models created specifically for the TBI population were developed in an attempt to estimate the occurrence of poor neurological prognosis using different outcomes. These so-called “prediction rules” are normally developed to determine the probability of a specific outcome to help physicians interpret clinical information.⁷⁵ However, depending on 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).

The first prediction rule was the GCS, a score so well-implemented in clinical practice as part of a standard clinical

Table 2: Important specific predictive models of prognosis in TBI

Author, period of data collect.	No. of patients	Data	Patient selection	Outcome	Predictors	Model	Validation	Performance
Choi et al., ¹² 1976-1989	555	Retrospective, single centre	GCS <9	GOS at 1 year	4 admission variables (Age, pupillary reactivity, motor response, intracerebral lesion)	Tree model	Limited	Accuracy: 78% (60%-82%)
Signorini et al., ²⁹ 1989-1991	372	Prospective, single centre	GCS ≤12 or >12 with ISS > 16	Mortality at 1 year	5 admission variables (Age, GCS, ISS, pupillary reactivity, hematoma on CT)	Logistic regression	Limited	Accuracy: 85%
Hsu et al., ⁷⁶ 1995-1998	3345	Database, multicentre	GCS ≤12	GOS in first 12 months	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)	Neural network	Yes	Accuracy: 76% Sensitivity: 48%-92% Specificity: 89%-99% (depending on the GOS score)
Andrews et al., ⁷⁷ 1989-1991	124	Prospective, single centre	GCS ≤12 or >12 with ISS > 15	GOS at 12 months	4 variables (time not reported) (Age, GCS, ISS, type of accident, referral, isolated head injury, CPP, hypotension, hypocarbia, sex, type of hematoma, evacuation of hematoma)	Tree model	No	Accuracy: 60%-64%
Rovlias et al., ¹⁷ 1993-2000	345	Prospective, single centre	GCS <9	GOS at 6 months	6 variables (time not reported) (Age, GCS, pupillary response, intracranial diagnosis, glucose level on day #2, SAH, WBC on admission)	Tree model	No	Accuracy: 87% Positive predictive Value for unfavourable outcome: 85%
Hukkelhoven et al., ¹³ 1991-1994	2269	2 RCTs, multicentre	GCS ≤12	GOS at 6 months	7 admission variables (Age, gender, cause of injury, motor score, pupillary reactivity, hypotension, hypoxia, CT classification, SAH)	Logistic regression	Yes	AUC* : 0.83-0.89
Combes et al., ⁷⁹ 1989-1992	132	Prospective, single centre	GCS <9	GOS (unclear time period)	3 admission variables (Age, motor response, hypoxia)	Logistic regression	No	Accuracy: 73% Sensitivity: 93% Specificity: 57%

GSC = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, ISS = Injury Severity Score

examination that we tend to forget that it is a specific prediction model developed in the TBI population.¹ Considering the limitations of the GCS (as previously discussed), other models were proposed for predicting short-, mid- and long-term outcomes of mortality or neurological functions.

In 1991, Choi and colleagues proposed one of the first prediction trees for severe head injury using the clinical and demographic variables of 555 patients on admission (pupillary response, age, motor response, intracerebral lesion) to predict the GOS at 12 months.¹² The predictive accuracy of the model was higher for good recovery (GOS 4 or 5) or death (GOS 1) with positive predictive value of 82%, than for intermediate neurological outcomes. Signorini et al used 5 admission characteristics (age, GCS, ISS, pupillary reactivity, and hematoma on CT scan) to derive a prediction rule of 85% accuracy to predict mortality at 1 year in moderate and severe TBI.²⁹ Their 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 et al derived and validated a rule to estimate the GOS assessed within 12 months after injury.⁷⁶ This neural network model was developed using 10 admission variables and obtained a global accuracy of 75.8% of GOS prediction. Despite a good specificity for worst outcomes on the GOS scale, this

accuracy is lower than that observed in previous studies. Moreover, close to 15% of the patients had better outcomes than predicted. 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.^{13,77} Hukkelhoven used data from 2 multicentre clinical trials previously performed in Europe and North America.^{13,78} 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, 2 or 3) at 6 months, revealed an accuracy that compared advantageously to the previously cited rules.

The use of potentially modifiable predictors (eg, hypoxia and hypotension) means that secondary brain injury components must be included. In a small prospective study (n = 124), Andrews et al evaluated the influence of variables leading to secondary brain injury to determine functional outcomes (GOS) at 12 months.⁷⁷ Three main prediction trees were created: one using only demographic data, a second using only injury data, and the third combining both types of variables. The accuracy of these tests ranged from 61% to 64% in the validation phase. A longer duration of insult correlated with a worst GOS for most of the injury data.

Many other studies have used relatively small sample sizes, precluding their application to populations other than the one for which they were developed. In addition, no other prediction rule generated better positive predictive values for poor or good mid- or long-term prognosis.^{17,79}

Conclusion

Over the last 2 decades, there has been a significant interest in the determination of prognosis post-TBI. However, long-term neurological prognosis post-TBI is difficult to evaluate early after the event despite the fact that many predictors of mortality and other long-term neurological outcomes have been identified. A few of the new diagnostic technologies are promising, but not yet ready for use in clinical practice. Since there are no predictors or diagnostic tests with clinically-significant positive predictive values for good or poor prognosis, many models and prediction rules were developed to improve this level of uncertainty. Most were more accurate in determining unfavourable outcomes, but none was precise enough to become a standard of care in the TBI population. Hospital mortality is probably the more precisely predicted outcome, but the low sensitivity of the models may signify that this marker only predicts the obvious.¹⁵

On the other hand, many limitations to these models and prediction rules have to be considered. First, many pre-date the CT scan advances in bedside care, monitoring, and consensus recommendations for TBI management.⁴ Additionally, very few models account for secondary cerebral injuries, which are not always avoidable despite appropriate prevention measures.^{4,13,77} Most prognostic models used admission variables, when it may be too early in the course of the disease to show high accuracy.⁸⁰ Other rules used complex formulas requiring computer software assistance, making their utilization less convenient in clinical practice.⁷⁶ More importantly, many models were derived from single centres,^{12,2} small cohorts,^{77,79} retrospective data,¹² or were never validated in a distinct dataset of patients,^{17,22,77} thus precluding generalizability of the findings.

In summary, actual models, generic or specific, are not accurate enough to help guide decision-making for therapy; however, physicians use scoring systems and predictive models in their practice.⁸¹ Thus, more precise prognostic instruments with long-term neurological outcome measures, along with mortality, have to be developed. These instruments will provide more accurate evidence-based expectations for physicians, the patient, and relatives. They will also enable better risk stratification for TBI patients, improve the evaluation of system performance, and help standardize future research into patients with TBI.

Alexis Turgeon, MD is an anesthesiologist and a critical care physician. He is currently a clinical scholar at the University of Ottawa.

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