Current Physical Medicine and Rehabilitation Reports (2020) 8:415–428
https://doi.org/10.1007/s40141-020-00298-w

BRAIN INJURY MEDICINE AND REHABILITATION (G GALANG, SECTION EDITOR)

Prognostication and Determinants of Outcome in Adults and Children with Moderate-to-Severe Traumatic Brain Injury

Justin Weppner[1] · William Ide[2] · Justin Tu[1] · Jacob Boomgaardt[1] · Albert Chang[3] · Stacy Suskauer[2,4]

Accepted: 8 October 2020 / Published online: 28 October 2020

Abstract

Purpose of Review It has been suggested in the literature that many physicians lack comfort in assessing prognosis following traumatic brain injury (TBI). The purpose of this review is to investigate the most recent work on predicting outcomes after moderate-to-severe TBI.

Recent Findings TBI is one of the leading causes of disability in the USA with an estimated 13.5 million individuals affected by varying severities of TBI. Many clinical variables, including age, admission Glasgow Coma Scale score, duration of posttraumatic amnesia, and duration of coma, have been studied to determine whether they play a role in outcome prediction. Newer variables being studied include serum biomarkers, abnormalities observed on magnetic resonance imaging, and data obtained from evoked potentials.

Summary The role of physiatry in evaluating patients following moderate-to-severe TBI is a valuable but difficult proposition. Appropriate distribution of acute treatment and rehabilitation resources is of utmost importance. For prognostication to be clinically useful, physiatrists must provide a reasonable impression of what life will be like for the patient in the longer term. In the future, additional work will be needed to better combine predictor variables tailored with precision to the patient to provide a clearer picture of individual outcomes following moderate-to-severe TBI.

Keywords Traumatic brain injury · Prognosis · Outcome · Prediction

Introduction

Traumatic brain injury (TBI) is one of the leading causes of disability in the USA with an estimated 13.5 million individuals affected by varying severities of TBI [1]. TBI is also a leading cause of acquired disability and mortality in the pediatric population. In 2014, over 837,000 TBI-related emergency department visits, hospitalizations, and deaths were estimated in American children by the Centers for Disease Control and Prevention [2]. Many survivors live with significant disabilities that are associated with a major socioeconomic burden. In 2010, the economic impact of TBI in the USA was estimated to be $76.5 billion in direct and indirect costs [3]. Accurate prognostication from physiatrists throughout the continuum of care from acute hospitalization through rehabilitation is important as it enables improved patient and family counseling, prioritizes rehabilitation goals, and justifies the allocation of healthcare resources.

TBI by nature is heterogeneous with no two injuries exactly alike. The patient's premorbid state of health, in addition to primary and secondary injury factors, affects how the patient will respond to the TBI. The defining outcome is also difficult to standardize with definitions of a "good" versus a "poor" outcome variable between studies. The Glasgow Outcome Scale (GOS) is popularly employed for its simplicity, but is

This article is part of the Topical Collection on *Brain Injury Medicine and Rehabilitation*

✉ Justin Weppner
jlw6en@virginia.edu

[1] Department of Physical Medicine and Rehabilitation, University of Virginia School of Medicine, Charlottesville, VA, USA

[2] Department of Physical Medicine & Rehabilitation, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[3] University of Virginia School of Medicine, Charlottesville, VA, USA

[4] Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

limited by its broad categories, which stratifies patients recovering from TBI into five groups depending upon their ability to perform activities of daily living and the amount of supervision required (Table 1) [4]. However, it can be argued that five outcome categories are insufficient to represent the wide range of mental and physical disability that a patient can have following TBI [5]. To better represent the patient's possible disability, the Glasgow Outcome Scale Extended (GOSE) further splits severe disability, moderate disability, and good recovery into upper and lower categories to allow for greater differentiation between levels of recovery [5, 6]. This gives greater sensitivity for detecting changes in condition over time and improves accuracy when assessing ongoing treatment or care needs (Table 2) [7]. Currently, there are no universally accepted scoring systems that reliably predict outcomes in patients following TBI.

The literature suggests that the majority of physicians do not feel knowledgeable to accurately assess prognosis in TBI [8]. Traditional predictors include demographic factors such as age, Glasgow Coma Scale (GCS) scores, length of coma, length of posttraumatic amnesia (PTA), and the presence of structural abnormalities on neuroimaging. Novel and emerging predictors include biomarkers and advanced magnetic resonance imaging (MRI). This article reviews the most recent work related to outcome prediction following moderate-to-severe TBI to improve physiatrists' ability to provide valuable prognostic information to patients and families (Table 3 and Fig. 1).

Overview of Potential Predictor Variables

Age

In the adult population, advanced age has been associated with worse outcomes in patients with severe TBI [9–12]. While some studies have identified threshold values for poor outcomes, other studies have treated the outcome as a continuous function of age [10, 11, 13, 14]. Hukkelhoven et al. examined four prospective series including 5600 patients and showed a linear association between age and both mortality and unfavorable outcome, which is defined as severe disability or vegetative state (VS) on the GOS [15]. It has been hypothesized that the adult brain has a decreased capacity for repair as it ages due to the declining number of functioning neurons combined with a diminished cognitive reserve [16, 17]. Overall, studies have shown that in the adult population, there is a linear association between advancing age and poorer functional outcome following severe TBI [15].

In the pediatric population, there are competing conceptions regarding the vulnerability of the developing brain to injury versus a child's enhanced capacity for neuroplasticity and recovery, which contributes to the lack of consensus on the impact of age on outcome upon TBI [18]. In general, children and adolescents have superior functional outcomes and rates of survival compared to adults sustaining severe TBI, though reports describing outcomes based on a child's age at injury are inconsistent [19•, 20]. Several studies evaluating intellectual function in TBI suggest lower IQ scores on initial testing and reduced recovery in infants and preschool-aged children compared to older children and adolescents over a 1–2-year follow-up period [21]. Keenan et al. reported high but relatively stable rates of attention deficit hyperactivity disorder and affective symptoms in children 6–11 years of age for 2 years after TBI; however, preschoolers demonstrated increasing symptoms over time, indicating variable symptom trajectories based on age at injury [22•]. This observation may be attributable, at least in part, to the lower demands on abstract or higher-level cognitive skills placed on children at younger developmental levels. Andruszkow et al. noted that children aged 0–7 years who sustained moderate-to-severe TBI had more favorable outcomes at 10-year follow-up compared to (a) older children and (b) adults as measured by the GOS but found no differences based on age at the time of injury for other physical and psychological outcome measures [23]. This finding may be impacted by the lower sensitivity of the GOS for detecting common impacts on children with TBI in comparison to more detailed and tailored measures such as the GOSE for Children [24]. Levin et al. reported variations in word fluency recovery based on age at time of injury as well

Table 1 The Glasgow Outcome Scale

Score	Description	
1	Death	
2	Vegetative state	
3	Severe disability	- Unable to live alone and requires the daily assistance of another person at home
4	Moderate disability	- Modified independent at home
		- Able to utilize public transportation
		- Able to work in a supported environment
5	Good recovery	- Able to resume normal occupational and social activities
		- There may be minor residual physical or psychological deficits

Table 2 Glasgow Outcome Scale Extended

Score	Description	
1	Death	
2	Vegetative state	
3	Severe disability—lower	- Patient requires frequent help or someone to be around most of the time
4	Severe disability—upper	- Does not need frequent help and is able to be at home alone for 8 h at a time - Not able to shop without assistance - Not able to travel locally without assistance
5	Moderate disability—lower	- Not able to work or only able to work in a sheltered noncompetitive position - Unable to participate in regular social or leisure activities outside home - Daily disruption of family relationships or friendships due to psychological problems
6	Moderate disability—upper	- Able to work or study but at a reduced capacity - Participates less than half as often in regular social and leisure activities outside of the home - Frequent but tolerable disruption of family and relationships or friendships due to psychological problems
7	Good recovery—lower	- Participates at least half as often as before injury in regular social and leisure activities outside of the home - Occasional disruption of family and relationships or friendships due to psychological problems - Symptoms related to the TBI affect daily life
8	Good recovery—upper	- Able to work at pre-TBI capacity - Able to resume regular social and leisure activities outside of the home - No psychological problems resulting in ongoing family disruption or disruption of friendships

as injury pattern (focal vs diffuse TBI). Younger children (mean age 7 years) with severe diffuse TBI displayed less improvement in word fluency over time compared to older children and adolescents, but younger children with focal left frontal lesions had less pronounced word fluency impairments compared to older children with similar focal injuries [25]. Interpretation of the literature is confounded by variable distributions of age categories and timing of follow-up as well as the potential influence of abusive head trauma that may have a delayed presentation in younger children and result from repeated insults [20].

Glasgow Coma Scale Score

The GCS has been widely used as a measure to record the level of consciousness and severity of injury in patients who have sustained a TBI (Table 4). GCS is an essential aspect of the primary trauma assessment and is monitored throughout the course of the acute hospitalization. The role of GCS in prognosticating outcomes following severe TBI has been extensively studied [26, 27]. There has been variability in the degree of correlation of initial GCS score with prognosis, with some studies finding a strong correlation of initial GCS score and long-term prognosis measured via the GOS, while other sources have noted a weak and somewhat inconsistent correlation [27–33]. This variability in outcome may be related to the fact that GCS is affected by numerous factors unrelated to the injuries such as alcohol, illicit drug intoxication, and sedative use. These limitations are most notable in patients with severe injuries as they are intubated and sedated, making accurate assessment more challenging [34–36]. Additionally, the timing of GCS measurement can impact the reliability of prognostic value, with the admission GCS found to be more reliable in terms of prognostication compared to the preadmission GCS [34–36].

In particular, the best motor response on admission is found to be the most useful GCS predictor of long-term functional outcome in patients with severe TBI [37]. Several studies have suggested that utilizing the motor component as an alternative to total GCS with similar prognostic value [38•, 39, 40]. This is most notable in those with severe injuries where verbal and eye responses are less reliable; thus, most of the predictive power of GCS is derived from the motor score [41•, 42]. While lower admission GCS score, particularly the motor response component, is associated with worse outcome, studies have shown mixed results regarding long-term outcome based on GCS alone given the wide range of confounding factors that may alter GCS scoring on admission.

IMPACT Prognostic Calculator

The IMPACT database includes patients with moderate-and-severe TBI (GCS ≤ 12) from eight randomized controlled trials and three observational studies conducted between 1984 and 1997 [43]. The intent of the IMPACT database was to produce a model that could be used to predict outcome after TBI at the point of admission to hospital. The investigators created three prognostic models: (1) the core model (age, motor score component from GCS, and pupillary reactivity), (2) the extended model (core model with addition of secondary insults [hypoxia and hypotension], CT findings, traumatic subarachnoid hemorrhage, and epidural hematoma), and (3) the lab model (extended model with additional information on hemoglobin and blood sugar). Validation of the model has

Table 3 Summary of predictor variables in adults

Variable	Summary
Age	- Linear association between advancing age and poorer functional outcome with older age associated with a worse outcome.
GCS	- Lower admission GCS scores, and in particular, the lower motor response is associated with a worse patient outcome.
CT	- Collapse of the basal cisterns is an indicator of increased intracranial pressure and is associated with an unfavorable outcome. - The presence of a midline shift of > 5 mm on the initial brain CT scan and a high- or mixed-density lesion > 25 cm^3 in volume have both been correlated with early death. - Marshall criteria (Table 5): - Diffuse brain injury I: associated with a good recovery (GOS 4 or 5). - Diffuse brain injury II combined with older age > 40 and the presence of multiple parenchymal lesions on CT scans: significantly correlated with poor outcome (GOS 1–3). - Diffuse brain injury III and IV groups: GCS score is the only significant prognostic factor, lower initial GCS of 3 to 5 correlated with poor outcome (GOS 1–3).
MRI	- Bilateral brainstem lesions make a good recovery unlikely on GOS. - Anterior and non-hemorrhagic lesions on MRI showed the highest positive predictive value for good outcome on the GOS.
DWI	- If MRI is completed in the initial 2 weeks following injury, a threshold ADC < 400×10^{-6} mm^2/s in 0.49% of brain tissue predicts a poor outcome (discharged to skilled nursing facility or died) versus a good outcome (discharged to inpatient rehabilitation or home).
DTI with MRS	- Combining diffusion tensor imaging (DTI) with magnetic resonance spectroscopy (MRS) has been shown to be 86% sensitive and 97% specific for predicting unfavorable outcome (death, persistent vegetative state, or minimally conscious state) 1 year after TBI.
Duration of Coma	- Duration of coma has been shown to have a near-linear relationship with duration of recovery time. - Length of coma greater than 4 weeks makes good recovery unlikely. - Severe disability is unlikely when duration of coma is less than 2 weeks.
Duration of PTA	- The longer the duration of PTA, the worse the patient outcome. - Per Katz et al.: - Severe disability is unlikely when PTA is less than 2 months. - Good recovery is unlikely when duration of PTA is greater than 3 months. - Per Walker et al.: - Duration of PTA ending within 4 weeks resulted in severe disability being unlikely at year 1, with good recovery being the most likely at year 2. - If PTA lasted beyond 8 weeks, good recovery was highly unlikely at year 1, and severe disability was about as likely if not more likely than moderate disability at year 2.
Biomarkers	- Serum levels of S100b, GFAP, UCH-L1, and SBDP150 predict unfavorable clinical outcomes (GOSE 1–4) assessed 6 months after moderate-to-severe acute TBI. - When all four biomarkers were above cutoff threshold, 77% experienced a poor outcome (GOSE 1–4).
SSEP	- Bilaterally normal SSEPs usually imply a good outcome. - Bilaterally absent SSEPs are strongly predictive of poor outcome. - SSEPs provide valuable complementary information to assist with the prediction of outcome in patients with severe TBI.

GCS, Glasgow Coma Scale

CT, computed tomography

GOS, Glasgow Outcome Scale

DWI, diffusion-weighted imaging

DTI, diffusion tensor imaging

MRS, magnetic resonance spectroscopy

PTA, posttraumatic amnesia

SSEP, somatosensory evoked potentials

shown that all IMPACT predictors have statistically significant associations with 6-month GOS in univariate and multivariable analyses. A poor outcome (GOS 1–3) occurred especially for those with GCS motor scores 1 or 2. Pupillary reactivity, hypoxia, and hypotension also had strong prognostic effects. Lower hemoglobin levels and higher glucose levels were associated with poor outcomes, but the effects were more moderate than other variables such as age [44].

Radiographic Imaging

Computed Tomography

Computed tomography (CT) is the preferred imaging modality for the acute evaluation of patients with moderate-to-severe TBI due to its availability, rapid image acquisition, and ability to detect fractures of the skull and intracranial hemorrhage that

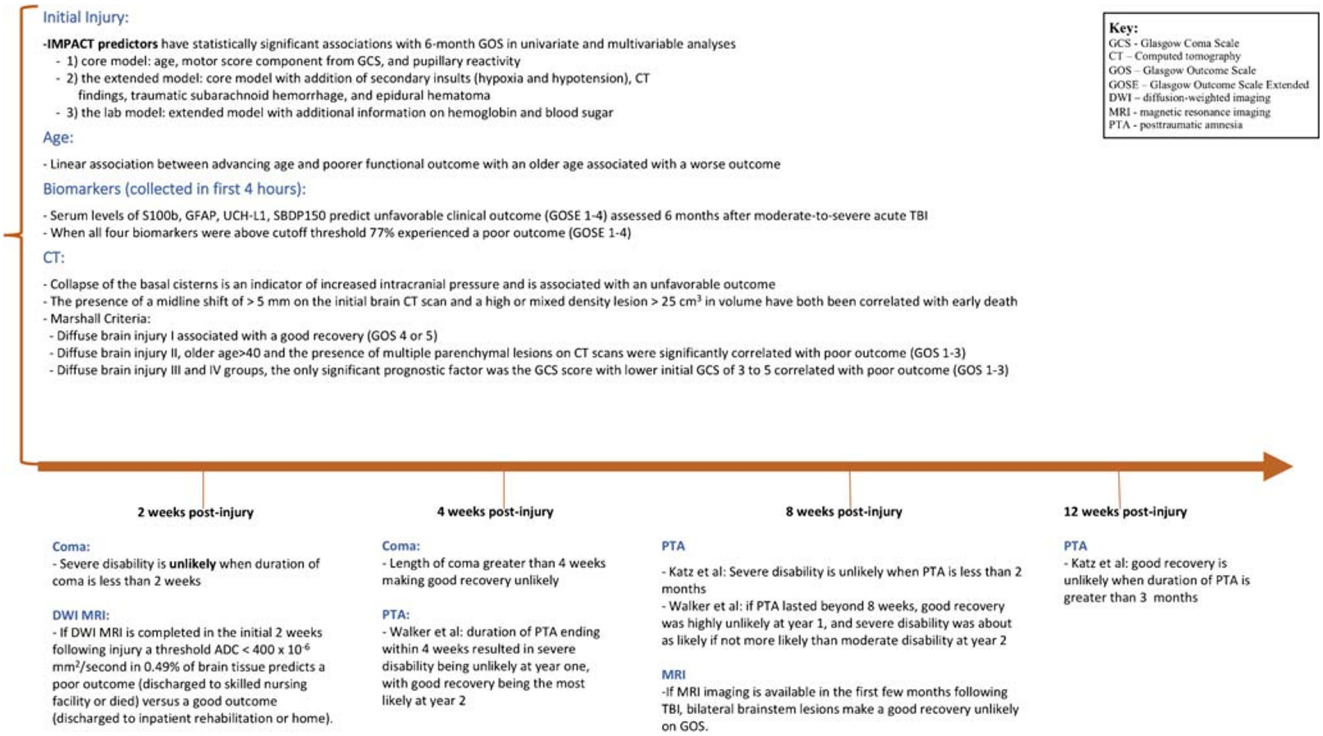

Fig. 1 Predictor variables of outcome in adults with TBI

require immediate neurosurgical attention. In patients with TBI, the outcome is better with the absence of intracranial abnormalities [45]. The presence of basal cistern collapse is an indicator of increased intracranial pressure and is associated with an unfavorable outcome following severe TBI [43, 46–52]. The Marshall CT classification system is a prognostic system that incorporates anatomical CT scan findings [53]. The Marshall CT classification uses CT scan findings on the status of the mesencephalic cisterns, the degree of midline shift, and the presence or absence of local lesions to categorize patients into six different groups (Table 5). The presence of a midline shift of > 5 mm on initial brain CT scan and a high- or mixed-density lesion > 25 cm^3 in volume have both been correlated with early death [54]. In patients with TBI, the Marshall criteria have been correlated with 6-month outcomes with all patients in the diffuse brain injury I group experiencing a good recovery (GOS 4 or 5). In the diffuse brain injury II group, older age > 40 and the presence of multiple parenchymal lesions on CT scans were significantly correlated with poor outcomes (GOS 1–3). For the diffuse brain injury III and IV groups, the only significant prognostic factor was the GCS score with lower initial GCS of 3 to 5 correlated with poor outcomes (GOS 1–3). Outcomes were unfavorable in most patients with intracerebral hematoma [55].

Table 4 The Glasgow Coma Scale

Feature	Response	Score
Best eye response	Open spontaneously	4
	Open to verbal command	3
	Open to pain	2
	No eye opening	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal output	1
Best motor response	Obeys commands	6
	Localizing to pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1

Magnetic Resonance Imaging

While CT is the initial imaging technique of choice in the setting of moderate-to-severe TBI, MRI is more sensitive in detailing traumatic lesions of the brain parenchyma, especially in the posterior fossa and identifying non-hemorrhagic lesions [51, 56–59, 60•]. Several published reports have proposed that brain stem lesions are a marker of poor prognosis following TBI. If MRI is available in the first few months following TBI, bilateral brainstem lesions make a good recovery unlikely on GOS [58–59, 60•, 61–63]. Anterior and non-hemorrhagic

Table 5 Marshall CT classification system for a head injury

Category	Description
Diffuse injury I (no visible pathology)	- No visible intracranial pathology observed on CT
Diffuse injury II	- Cisterns are present with midline shift of 0–5 mm
	- No high- or mixed-density lesion > 25 cm^3
	- May include bone fragments and foreign bodies
Diffuse injury III (swelling)	- Cisterns compressed or absent with midline shift of 0–5 mm
	- No high- or mixed-density lesion > 25 cm^3
Diffuse injury IV (shift)	- Midline shift > 5 mm
	- No high- or mixed-density lesion > 25 cm^3
Diffuse injury V	- Any lesion surgically evacuated
Diffuse injury VI	- High- or mixed-density lesion > 25 cm^3; not surgically evacuated

lesions on MRI showed the highest positive predictive value for a good outcome on the GOS [60•].

Quantitative Diffusion-Weighted MRI

Diffusion-weighted imaging (DWI) is a specific MRI sequence, based on the changes in the diffusion of water molecules in brain tissue, which is sensitive to brain ischemia. Restricted diffusion is seen when there is cell death due to significant tissue injury and combining images obtained with different amounts of diffusion weighting producing a diffusion coefficient (ADC) map. The ADC is sensitive to acute and subacute TBI and has been shown to provide prognostic information [64•]. If MRI is completed in the initial 2 weeks following injury, a threshold ADC < 400×10^{-6} mm^2/s in 0.49% of brain tissue predicts a poor outcome (discharged to a skilled nursing facility or died) versus a good outcome (discharged to inpatient rehabilitation or home) [64•]. While the initial investigation has shown some preliminary promising results, large prospective studies that track patient outcome over a longer period are necessary to better elucidate the prognostic role of quantitative diffusion-weighted MRI in moderate-to-severe TBI.

Diffusion Tensor Imaging and Magnetic Resonance Spectroscopy

Combining diffusion tensor imaging (DTI) with magnetic resonance spectroscopy (MRS) has been shown to be 86% sensitive and 97% specific for predicting unfavorable outcomes (death, persistent VS, or minimally conscious state (MCS)) 1 year after TBI [65]. DTI is a relatively new imaging technique that can be used to evaluate white matter in the brain detailing the orientation and direction of white matter fiber tracts. This method involves quantifying the orientation and directional uniformity of water diffusion in brain tissue. In white matter, the mobility of water is restricted in directions perpendicular to the axons oriented along the fiber tracts, and thus, the orientation and direction of these fibers can be traced. MRS differs from conventional MRI in that the information from protons in water is suppressed, allowing proton signals from other metabolites to be measured. The use of multimodal magnetic resonance techniques combining DTI with MRS imaging performed in the subacute period following severe TBI provides valuable information on both primary and secondary brain injuries, assessment of metabolic changes within the brain, and prognostic information on the unfavorable outcome at 1 year [65].

Coma

The duration of coma has been shown to have a near-linear relationship with duration of recovery time following TBI with diffuse axonal injury without focal cortical injury [66]. Prolonged duration of coma portends a worse outcome following severe TBI with a length of coma greater than 4 weeks making good recovery unlikely, while severe disability is improbable when it is less than 2 weeks [4, 67••].

Further evidence has demonstrated that a more favorable prognosis is observed in those who have both traumatic etiologies and diagnosis of a MCS as opposed to a VS at the time of inpatient rehabilitation admission [68–70]. Additionally, it has been shown that patients admitted to inpatient rehabilitation at a VS or MCS level of recovery were able to generally progress beyond the post-confusion level. This occurred even if patients had MCS of 3 months or longer. Nearly half of patients with long-term follow-up achieved recovery to safe, daytime independence at home, and 22% returned to work or school within 2 years after injury. A noteworthy proportion (17%) returned to productive pursuits at or near their previous level of functioning. Overall, there was a favorable prognosis for the continued evolution of recovery to post-confusion levels for patients with prolonged, severe disorders of consciousness [69].

Posttraumatic Amnesia

PTA is a period of time after a TBI when the brain is unable to form continuous day-to-day memories. The Galveston Orientation and Amnesia Test (GOAT) is a tool developed to evaluate cognition serially during the subacute stage of recovery from TBI [71]. This scale measures orientation to person, place, and time and memory for events preceding and following the injury. The duration of PTA is defined as the period following a coma in which the GOAT score is < 75. PTA is considered to have ended if a score ≥ 75 is achieved on two consecutive administrations [72, 73]. The orientation log (O-Log) is a brief measure of orientation as an alternative to the GOAT. An advantage of this brief measure is ease of administration, provision for cueing if the patient is not able to respond or responds inaccurately, consistent scoring across items, and exclusion of questions pertaining to personal information or hard-to-verify amnesia-related items [74]. The duration of PTA is defined as the period following a coma in which the O-Log score is < 25. PTA is considered to have ended if a score ≥ 25 is achieved on two consecutive administrations.

Classically, PTA duration has been a powerful prognostic factor and has been particularly useful for inpatient rehabilitation physicians managing patients recovering from severe TBI as many recovery thresholds are crossed during a stay at an inpatient rehabilitation facility [4, 67••]. The longer the duration of PTA, the worse the patient outcome with severe disability unlikely when PTA is less than 2 months, though good recovery is unlikely when PTA duration is greater than 3 months [67••]. More recently, upon further evaluation of the relationship between PTA duration and patient outcome, PTA duration ending within 4 weeks resulted in severe disability being unlikely at year 1, with good recovery being the most likely at year 2. Conversely, if PTA lasted beyond 8 weeks, good recovery was highly unlikely at year 1, and severe disability was about as likely if not more likely than moderate disability at year 2 [75••]. In addition to improved outcome from year 1 to year 2, there is evidence that patients with a shorter PTA duration may experience continued late improvement between year 2 and year 5 [76].

Expanding on the GOS as a measure of the level of disability and global neurological functional outcome following TBI, the GOSE is the recommended core global measurement in TBI research [7, 77–80]. The PTA duration and its effect on GOSE scores at 1, 2, 5, and 10 years post-injury have been assessed. Compared to previous threshold values outlined, patients with PTA duration less than 18 days were found to have increased GOSE scores at the 1-, 2-, and 5-year intervals compared to those with PTA greater than 19 days [81].

Further illustrating the importance of PTA duration and its impact on functional outcomes, a study followed patients at 1-, 2-, and 5-year intervals post-injury after having moderate-to-severe TBI and being discharged from a rehabilitation facility [82•]. The functional independence measure (FIM) instrument was used to evaluate outcomes, allowing for interpretation of the required hours of care and subsequently the burden of care [83, 84]. Patients were divided into either having non-extremely severe PTA (≤ 28 days) or extremely severe PTA (> 28 days). Ultimately, those with non-extremely severe PTA were noted to have higher FIM scores at all time points relative to those with extremely severe PTA [82•]. These results can further supplement the previously described threshold values discussed earlier.

PTA duration has a significant impact on other prognostic measures, including a return to work (RTW) and intelligence. Specifically, PTA duration of 12.1 days for those with moderate or severe TBI predicted early RTW (i.e., within 6 months of injury), whereas patients with PTA duration of 26.2 days had a late RTW [85•]. These findings were elaborated further with decreased probability of employment at 1-, 2-, and 5-year follow-up of patients with moderate-to-severe TBI with increased PTA duration [86].

Regarding intelligence, a large meta-analysis showed that PTA duration can help predict potential declines in intelligence. Patients with severe TBI and increased PTA duration were found to have significantly larger depressions in IQ domains, specifically full-scale IQ, performance IQ, and verbal IQ [87]. Previously, evidence has suggested that predictive value of PTA duration for intelligence is superior to that of either GCS scores or coma duration [88, 89].

The above evidence suggests the importance of using PTA duration to prognosticate patients with severe TBI with respect to multiple domains. Despite evidence demonstrating the importance of the length of coma and prognosticating TBI, PTA duration has been described as a significant unique predictor of patient FIM score at discharge, whereas duration of coma was not [90]. PTA duration remains the most robust injury severity predictor of long-term outcomes following TBI, demonstrating to predict the degree of recovery [67••, 75••], the severity of disability [75••], ability to anticipate traffic hazards [91], independent living status after 1 year [92], and RTW [85•, 86, 93].

Biomarkers

S100B

S100B is an astrocytic protein specific to the central nervous system with serum and cerebrospinal fluid (CSF) levels increasing following TBI. Some studies have questioned the validity of S100B levels as a reliable prognostication tool citing confounding extracerebral origins from long bone fractures, variable collection timing in relation to injury, and strategies employed in the literature to correlate S100B levels to a patient outcome [94–102]. Serum and CSF levels are elevated

early across the first 6 days following severe TBI and diminish over time. It has been shown that subjects with higher CSF S100B concentration in the first week following injury had a higher acute mortality and worse GOS and Disability Rating Scale (DRS) scores at 6 months post-injury. Higher mean and peak serum S100B levels were predictors of acute mortality following severe TBI [103].

Glial Fibrillary Acidic Protein

Glial fibrillary acidic protein (GFAP) is a monomeric intermediate filament protein of astrocytes that may be measured in serum or CSF samples. Median serum GFAP has been shown to be high in patients who died following severe TBI compared with patients who were alive at 6 months post-injury. Patients with a poor outcome (GOS 1–3) had higher serum concentrations of GFAP than those patients with good outcome (GOS 4 or 5) at 6 months post-injury [97]. Persistent elevation of GFAP on day 2 following TBI is predictive of increased mortality [104].

Ubiquitin C-Terminal Hydrolase L1

Ubiquitin C-terminal hydrolase L1 (UCH-L1) is a deubiquitinating enzyme that is selectively expressed in the brain and is required for synaptic function. Elevated CSF levels of UHC-L1 in the first week post severe TBI were associated with increased mortality at 6 weeks post-injury and poor outcome (GOS 1–3) at 6 months post-injury [105]. Serum UCH-L1 levels in the first 7 days have been shown to independently predict mortality in the severe TBI population [106].

Additional study has shown that serum levels of S100B, GFAP, UCH-L1, and SBDP150 biomarkers predict unfavorable clinical outcomes (GOSE 1–4) assessed 6 months after moderate-to-severe acute TBI. When all four biomarkers were above cutoff threshold, 77% of subjects experienced a poor outcome (GOSE 1–4), while 22% experienced a poor outcome when all four biomarkers were below the cutoff threshold. Elevations of S100B, GFAP, UCH-L1, and SBDP150 levels early following moderate-to-severe TBI independently predicted outcome. A predictive model combining S100B and GFAP levels with patient variables including age, sex, GCS, and CT findings provides a sensitivity of 67% and specificity of 83% in predicting a poor outcome (GOSE 1–4) [107••].

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) may serve as a prognostic tool in the severe TBI population. The median nerve is stimulated at the wrist, and recordings are obtained at key locations from the neck at the level of C-2 (N13 potential) and the scalp (N20 potential). The peak latencies of N13 and N20 potentials may be used to calculate the peak-to-peak central conduction time (CCT), and using Judson's protocol, CCT may be classified as normal, increased latency (> 7 ms in patients < 50 years of age or > 7.3 ms in patients > 50 years of age or difference between sides > 0.8 ms), unilaterally absent, or bilaterally absent [108]. Since 1979, there have been several studies documenting the use of SSEP monitoring to help predict the outcome of patients who have suffered severe TBI [109–114]. Judson et al. studied 100 adults with severe TBI and found that if the SSEPs were absent bilaterally, the outcome was always death or a VS [108]. Blinded review SSEPs for 105 TBI patients revealed that SSEP monitoring in the ICU provides a reliable predictor of outcome following severe TBI. It has been shown that 60% of patients can expect a good outcome if CCT is normal bilaterally and the chances of death are less than 10% [113]. In contrast to the anoxic brain injury population, the presence of normal SSEPs is an indicator of awakening from a coma and good outcome [115]. Unilateral or bilateral increased CCT latency decreases the chance of a good outcome to less than 30%, and if an N20 is absent, the likely outcome is severe disability, VS, or death [113]. Bilateral loss of N20s has been thought to be a reliable marker of poor prognosis. Performing SSEPs early following injury and performing only one SSEP examination in cases of bilateral loss of N20s may lead to an underestimate of long-term functional recovery, and repeat SSEPs should be considered in the early acute phase of severe TBI. Confounding factors that should be considered when interpreting SSEPs include (1) cervical cord injury, (2) the presence of a scalp hematoma that would reduce the amplitude of the cortical potential, (3) brainstem hemorrhage, and (4) muscle activity [113]. As a consequence, caution is warranted in predicting a poor prognosis based predominantly on SSEPs in patients with TBI and should be considered in the overall clinical picture [116–119].

Overall, studies have indicated that (1) bilaterally normal SSEPs usually imply a good outcome, (2) bilaterally absent SSEPs are strongly predictive of poor outcome, and (3) SSEPs provide valuable complementary information to assist with the prediction of outcome in patients with severe TBI.

Predictor Variables in the Pediatric Population

Severe pediatric TBI is associated with estimated 16–22% mortality and 50.6% rate of unfavorable outcomes at 6 months [20, 120]. Healthcare-related quality of life across multiple dimensions is diminished in up to 40% of children 12 months following moderate or severe TBI [121]. In addition to persistent physical impairments, traumatic injury to the developing brain is of particular concern and reflected in neuropsychological and academic impairments following TBI in young children [122, 123].

Outcome prognostication in children with TBI is challenging and influenced by multiple factors to include injury severity, mechanism, age, the presence of concomitant injuries, physiological factors, social and family characteristics, and trajectory of early recovery [19•, 20, 121, 124]. Injury severity represented by the GCS score, particularly that obtained post-resuscitation, has been shown to have reliable predictive power [124]. A retrospective cohort study of 888 patients with severe TBI found mortality rates decreased as GCS scores increased (GCS 3, 53% mortality; GCS 5, ~ 9% mortality; GCS 8, ~ 3% mortality) in children aged ≤ 15 years [19•]. Hypothermia (temperature less than 36 °C) at presentation in combination with bilateral fixed and dilated pupils and a GCS of 3 confers the greatest TBI mortality risk [125]. Though children with severe injuries (GCS 3–4) have high rates of death and severe disability, 14.9% had good long-term global outcomes defined by the achievement of independent living, employment, or academic participation with minimal neurologic or cognitive deficits [125].

As has been well defined in adults, longer PTA duration is associated with less favorable outcomes in pediatric TBI. The validated scale specifically developed for assessing PTA in children is the Children's Orientation and Amnesia Test (COAT) [126]. An additional tool often utilized for the assessment of PTA in adolescents is the O-Log [74]. A child is deemed to have emerged from PTA on the first of two consecutive days on which the COAT score falls within the average range for the child's age [126]. A systematic review evaluating school-aged children (6–18 years) with TBI found that longer PTA duration is associated with worse outcomes in global functioning, memory, problem-solving, executive functioning, social functioning, academic performance, independent living skills, and self-care [126]. In most studies, PTA duration was a stronger predictor of outcomes than GCS or length of coma [126]. An additional recovery milestone with prognostic utility is the time from injury to following commands (TFC). TFC often occurs during the acute phase of recovery and is associated with poorer outcomes if extending beyond 26 days [124, 127, 128].

The health and function of the family unit are instrumental in child development and have been shown to play a significant role in TBI recovery. Lower socioeconomic status and increased parental stress not only are risk factors for sustaining TBI in childhood but also influence recovery as essential environmental factors [129]. Restricted family access to financial and social resources is associated with impaired intellectual function in children after TBI [129, 130]. Positive family function, including parent psychological functioning and communication skills, is associated with improved psychosocial and behavioral outcomes [17, 21, 22•, 129]. Neuroimaging in pediatric TBI provides useful diagnostic information and can also be utilized for outcome prediction. CT is the most frequently utilized and appropriate modality for initial evaluation of TBI but may only reveal 30–60% of lesions identified by standard MRI [131]. Studies have examined the impact of injury burden with respect to total lesion volume as well as anatomic location and depth of brain regions affected on outcomes in pediatric TBI. Greater fluid-attenuated inversion recovery (FLAIR) hyperintensity total lesion volume correlated with worse GOSE Pediatric scores and IQ at 12 months, as did the presence of lesions in all three anatomic zones of the brain (cortical, middle, and brainstem) compared to lesions isolated to higher zones [131]. Deeper lesions are also associated with lower GCS scores, and lesion depth is most predictive when assessed at the time of discharge from rehabilitation compared to a 1-year follow-up [132].

Conclusions

The role of physiatry in evaluating patients following moderate-to-severe TBI is a valuable but difficult proposition. Appropriate distribution of acute treatment and rehabilitation resources is of utmost importance. For prognostication to be clinically useful, outcomes must provide a reasonable impression of what life will be like for the patient in the longer term. Dichotomizing outcomes into "good" or "poor" may not be accurate enough to provide granularity to counsel patients or their families sufficiently. The needs of families should be considered in future research and it is important that researchers consider the types of prognostic information that families desire. In the future, additional work will be needed to better combine predictor variables tailored with precision to the patient to provide a clearer picture of individual outcome following moderate-to-severe TBI.

Compliance with Ethical Standards

Conflict of Interest The authors declare no that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Schiller JS, Lucas JW, Ward BW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview survey, 2010. Vital Health Stat. 2012;10(252):1–207.

2. Peterson B, Xu L, Daugherty J, Breiding J. Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths, United States, 2014. 2019. https://www.cdc.gov/traumaticbraininjury/pdf/TBI-Surveillance-Report-FINAL_508.pdf.
3. Finkelstein E, Corso PS, Miller TR. The incidence and economic burden of injuries in the United States. Oxford ; New York: Oxford University Press; 2006. xiii, 187 p. p
4. Kothari S, DiTommaso C. Chapter 18: Prognosis after severe traumatic brain injury: a practical, evidence-based approach. In: Zasler ND, Katz DI, Zafonte RD, editors. Brain injury neducube: principles and practice, 2nd ed. Demos Medical; 2013. p. 248–78.
5. Weir J, Steyerberg EW, Butcher I, Lu J, Lingsma HF, McHugh GS, et al. Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale? J Neurotrauma. 2012;29(1):53–8. https://doi.org/10.1089/neu.2011.2137.
6. Pretz CR, Dams-O'Connor K. Longitudinal description of the Glasgow Outcome Scale-extended for individuals in the traumatic brain injury model systems national database: a National Institute on Disability and Rehabilitation Research traumatic brain injury model systems study. Arch Phys Med Rehabil. 2013;94(12):2486–93. https://doi.org/10.1016/j.apmr.2013.06.021.
7. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma. 1998;15(8):573–85. https://doi.org/10.1089/neu.1998.15.573.
8. Perel P, Wasserberg J, Ravi RR, Shakur H, Edwards P, Roberts I. Prognosis following head injury: a survey of doctors from developing and developed countries. J Eval Clin Pract. 2007;13(3):464–5. https://doi.org/10.1111/j.1365-2753.2006.00713.x.
9. Braakman R, Gelpke GJ, Habbema JD, Maas AI, Minderhoud JM. Systematic selection of prognostic features in patients with severe head injury. Neurosurgery. 1980;6(4):362–70.
10. Choi SC, Ward JD, Becker DP. Chart for outcome prediction in severe head injury. J Neurosurg. 1983;59(2):294–7. https://doi.org/10.3171/jns.1983.59.2.0294.
11. Gómez PA, Lobato RD, Boto GR, De la Lama A, González PJ, de la Cruz J. Age and outcome after severe head injury. Acta Neurochir. 2000;142(4):373–80; discussion 80-1. https://doi.org/10.1007/s007010050445.
12. Signorini DF, Andrews PJ, Jones PA, Wardlaw JM, Miller JD. Predicting survival using simple clinical variables: a case study in traumatic brain injury. J Neurol Neurosurg Psychiatry. 1999;66(1):20–5. https://doi.org/10.1136/jnnp.66.1.20.
13. Narayan RK, Greenberg RP, Miller JD, Enas GG, Choi SC, Kishore PR, et al. Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. J Neurosurg. 1981;54(6):751–62. https://doi.org/10.3171/jns.1981.54.6.0751.
14. Teasdale G, Skene A, Parker L, Jennett B. Age and outcome of severe head injury. Acta Neurochir Suppl (Wien). 1979;28(1):140–3. https://doi.org/10.1007/978-3-7091-4088-8_33.
15. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg. 2003;99(4):666–73. https://doi.org/10.3171/jns.2003.99.4.0666.
16. Marshall LF. Head injury: recent past, present, and future. Neurosurgery. 2000;47(3):546–61. https://doi.org/10.1097/00006123-200009000-00002.
17. Peterson DA. Stem cells in brain plasticity and repair. Curr Opin Pharmacol. 2002;2(1):34–42. https://doi.org/10.1016/s1471-4892(01)00118-7.
18. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. Brain. 2011;134(Pt 8):2197–221. https://doi.org/10.1093/brain/awr103.
19.• Emami P, Czorlich P, Fritzsche FS, Westphal M, Rueger JM, Lefering R, et al. Impact of Glasgow Coma Scale score and pupil parameters on mortality rate and outcome in pediatric and adult severe traumatic brain injury: a retrospective, multicenter cohort study. J Neurosurg. 2017;126(3):760–7. https://doi.org/10.3171/2016.1.JNS152385 **This retrospective cohort analysis of severe TBI patients registered in the Trauma Registry of the German Society for Trauma Surgery between 2002 and 2013. A total of 9959 patients satisfied inclusion criteria; 888 (8.9%) patients were ≤ 15 years old (median 10 years). This study found that severe TBI in children aged ≤ 15 years is associated with a lower mortality rate and superior functional outcome than in adults.**
20. Au AK, Clark RSB. Paediatric traumatic brain injury: prognostic insights and outlooks. Curr Opin Neurol. 2017;30(6):565–72. https://doi.org/10.1097/WCO.0000000000000504.
21. Ewing-Cobbs L, Barnes MA, Fletcher JM. Early brain injury in children: development and reorganization of cognitive function. Dev Neuropsychol. 2003;24(2–3):669–704. https://doi.org/10.1080/87565641.2003.9651915.
22.• Keenan HT, Clark AE, Holubkov R, Cox CS, Ewing-Cobbs L. Psychosocial and executive function recovery trajectories one year after pediatric traumatic brain injury: the influence of age and injury severity. J Neurotrauma. 2018;35(2):286–96. https://doi.org/10.1089/neu.2017.5265 **Prospective cohort study of 519 children with either TBI or orthopedic injury age 2.5–15 years. Children's psychosocial and executive function outcomes at 3 and 12 months post-injury were examined. Children with TBI have differing trajectories of recovery and development of new problems dependent on their injury severity and developmental stage at injury. Younger age at injury was associated with poorer outcomes in emotional functioning, behavior regulation, and metacognition indices, which all contribute to later school success.**
23. Andruszkow H, Deniz E, Urner J, Probst C, Grün O, Lohse R, et al. Physical and psychological long-term outcome after traumatic brain injury in children and adult patients. Health Qual Life Outcomes. 2014;12:26. https://doi.org/10.1186/1477-7525-12-26.
24. Beers SR, Wisniewski SR, Garcia-Filion P, Tian Y, Hahner T, Berger RP, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. J Neurotrauma. 2012;29(6):1126–39. https://doi.org/10.1089/neu.2011.2272.
25. Levin HS. Neuroplasticity following non-penetrating traumatic brain injury. Brain Inj. 2003;17(8):665–74. https://doi.org/10.1080/0269905031000107151.
26. McNett M. A review of the predictive ability of Glasgow Coma Scale scores in head-injured patients. J Neurosci Nurs. 2007;39(2):68–75. https://doi.org/10.1097/01376517-200704000-00002.
27. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol. 2014;13(8):844–54. https://doi.org/10.1016/S1474-4422(14)70120-6.
28. Demetriades D, Kuncir E, Murray J, Velmahos GC, Rhee P, Chan L. Mortality prediction of head Abbreviated Injury Score and Glasgow Coma Scale: analysis of 7,764 head injuries. J Am Coll Surg. 2004;199(2):216–22. https://doi.org/10.1016/j.jamcollsurg.2004.02.030.
29. Foreman BP, Caesar RR, Parks J, Madden C, Gentilello LM, Shafi S, et al. Usefulness of the abbreviated injury score and the injury severity score in comparison to the Glasgow Coma Scale in predicting outcome after traumatic brain injury. J Trauma. 2007;62(4):946–50. https://doi.org/10.1097/01.ta.0000229796.14717.3a.

30. Benzer A, Mitterschiffthaler G, Marosi M, Luef G, Pühringer F, De La Renotiere K, et al. Prediction of non-survival after trauma: Innsbruck Coma Scale. Lancet. 1991;338(8773):977–8.
31. Jiang JY, Gao GY, Li WP, Yu MK, Zhu C. Early indicators of prognosis in 846 cases of severe traumatic brain injury. J Neurotrauma. 2002;19(7):869–74. https://doi.org/10.1089/08977150260190456.
32. Dikmen SS, Machamer JE, Powell JM, Temkin NR. Outcome 3 to 5 years after moderate to severe traumatic brain injury. Arch Phys Med Rehabil. 2003;84(10):1449–57. https://doi.org/10.1016/s0003-9993(03)00287-9.
33. Lannoo E, Van Rietvelde F, Colardyn F, Lemmerling M, Vandekerckhove T, Jannes C, et al. Early predictors of mortality and morbidity after severe closed head injury. J Neurotrauma. 2000;17(5):403–14. https://doi.org/10.1089/neu.2000.17.403.
34. Langfitt TW. Measuring the outcome from head injuries. J Neurosurg. 1978;48(5):673–8. https://doi.org/10.3171/jns.1978.48.5.0673.
35. Waxman K, Sundine MJ, Young RF. Is early prediction of outcome in severe head injury possible? Arch Surg. 1991;126(10):1237–41; discussion 42. https://doi.org/10.4103/2229-5151.190650.
36. Stocchetti N, Pagan F, Calappi E, Canavesi K, Beretta L, Citerio G, et al. Inaccurate early assessment of neurological severity in head injury. J Neurotrauma. 2004;21(9):1131–40. https://doi.org/10.1089/neu.2004.21.1131.
37. Kouloulas EJ, Papadeas AG, Michail X, Sakas DE, Boviatsis EJ. Prognostic value of time-related Glasgow coma scale components in severe traumatic brain injury: a prospective evaluation with respect to 1-year survival and functional outcome. Int J Rehabil Res. 2013;36(3):260–7. https://doi.org/10.1097/MRR.0b013e32835fd99a.
38.• Chou R, Totten AM, Carney N, Dandy S, Fu R, Grusing S, et al. Predictive utility of the total Glasgow Coma Scale Versus the motor component of the Glasgow Coma Scale for identification of patients with serious traumatic injuries. Ann Emerg Med. 2017;70(2):143–57.e6. https://doi.org/10.1016/j.annemergmed.2016.11.032 **Meta-analysis was conducted to compare the predictive utility of the total GCS versus the motor GCS or Simplified Motor Scale in field triage of trauma. 18 head-to-head studies of predictive utility were reviewed. The total GCS is associated with slightly greater discrimination than the motor GCS or Simplified Motor Scale for identifying severe trauma. The small differences in discrimination are likely to be clinically unimportant.**
39. Healey C, Osler TM, Rogers FB, Healey MA, Glance LG, Kilgo PD, et al. Improving the Glasgow Coma Scale score: motor score alone is a better predictor. J Trauma. 2003;54(4):671–8; discussion 8-80. https://doi.org/10.1097/01.TA.0000058130.30490.5D.
40. Lesko MM, Jenks T, O'Brien SJ, Childs C, Bouamra O, Woodford M, et al. Comparing model performance for survival prediction using total Glasgow Coma Scale and its components in traumatic brain injury. J Neurotrauma. 2013;30(1):17–22. https://doi.org/10.1089/neu.2012.2438.
41.• Reith FCM, Lingsma HF, Gabbe BJ, Lecky FE, Roberts I, Maas AIR. Differential effects of the Glasgow Coma Scale Score and its components: an analysis of 54,069 patients with traumatic brain injury. Injury. 2017;48(9):1932–43. https://doi.org/10.1016/j.injury.2017.05.038 **The study aimed to investigate the contribution of the GCS components to the sum score, floor and ceiling effects of the components, and their prognostic effects. Data on adult TBI patients were gathered from three data repositories: TARN ($n = 50,064$), VSTR ($n = 14,062$), and CRASH ($n = 9941$). The GCS components contribute differentially across the spectrum of consciousness to the sum score. The specific component-profile is related to outcome and the three components combined contain higher prognostic value than the sum score across different TBI severities. The investigators recommend a multidimensional use of the three-component GCS both in clinical practice, and in prognostic studies.**
42. Cheng K, Bassil R, Carandang R, Hall W, Muehlschlegel S. The estimated verbal GCS subscore in intubated traumatic brain injury patients: is it really better? J Neurotrauma. 2017;34(8):1603–9. https://doi.org/10.1089/neu.2016.4657.
43. Maas AI, Steyerberg EW, Butcher I, Dammers R, Lu J, Marmarou A, et al. Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24(2):303–14. https://doi.org/10.1089/neu.2006.0033.
44. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008;5(8):e165; discussion e. https://doi.org/10.1371/journal.pmed.0050165.
45. Chesnut RM. Evolving models of neurotrauma critical care: an analysis and call to action. Clin Neurosurg. 2000;46:185–95.
46. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2005;57(6):1173–82; discussion −82. https://doi.org/10.1227/01.neu.0000186013.63046.6b.
47. Eisenberg HM, Gary HE, Aldrich EF, Saydjari C, Turner B, Foulkes MA, et al. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1990;73(5):688–98. https://doi.org/10.3171/jns.1990.73.5.0688.
48. van Dongen KJ, Braakman R, Gelpke GJ. The prognostic value of computerized tomography in comatose head-injured patients. J Neurosurg. 1983;59(6):951–7. https://doi.org/10.3171/jns.1983.59.6.0951.
49. Selladurai BM, Jayakumar R, Tan YY, Low HC. Outcome prediction in early management of severe head injury: an experience in Malaysia. Br J Neurosurg. 1992;6(6):549–57. https://doi.org/10.3109/02688699209002372.
50. Liu HM, Tu YK, Su CT. Changes of brainstem and perimesencephalic cistern: dynamic predictor of outcome in severe head injury. J Trauma. 1995;38(3):330–3. https://doi.org/10.1097/00005373-199503000-00003.
51. Kakarieka A, Braakman R, Schakel EH. Classification of head injuries based on computerized tomography: prognostic value. Neurologia. 1995;10(4):159–61.
52. Servadei F, Nasi MT, Giuliani G, Cremonini AM, Cenni P, Zappi D, et al. CT prognostic factors in acute subdural haematomas: the value of the 'worst' CT scan. Br J Neurosurg. 2000;14(2):110–6. https://doi.org/10.1080/02688690050004525.
53. Marshall LF, Marshall SB, Klauber MR, Van Berkum CM, Eisenberg H, Jane JA, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma. 1992;9(Suppl 1):S287–92.
54. Rapenne T, Lenfant F, N'Guyen Kim L, Honnart D, Beaurain J, Freysz M. Predictive factors of short-term mortality in patients with severe head injury. Presse Med. 1997;26(35):1661–5.
55. Ono J, Yamaura A, Kubota M, Okimura Y, Isobe K. Outcome prediction in severe head injury: analyses of clinical prognostic factors. J Clin Neurosci. 2001;8(2):120–3. https://doi.org/10.1054/jocn.2000.0732.
56. Mannion RJ, Cross J, Bradley P, Coles JP, Chatfield D, Carpenter A, et al. Mechanism-based MRI classification of traumatic brainstem injury and its relationship to outcome. J Neurotrauma. 2007;24(1):128–35. https://doi.org/10.1089/neu.2006.0127.
57. Chastain CA, Oyoyo UE, Zipperman M, Joo E, Ashwal S, Shutter LA, et al. Predicting outcomes of traumatic brain injury by

imaging modality and injury distribution. J Neurotrauma. 2009;26(8):1183–96. https://doi.org/10.1089/neu.2008.0650.

58. Firsching R, Woischneck D, Diedrich M, Klein S, Rückert A, Wittig H, et al. Early magnetic resonance imaging of brainstem lesions after severe head injury. J Neurosurg. 1998;89(5):707–12. https://doi.org/10.3171/jns.1998.89.5.0707.
59. Kampfl A, Schmutzhard E, Franz G, Pfausler B, Haring HP, Ulmer H, et al. Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. Lancet. 1998;351(9118):1763–7. https://doi.org/10.1016/S0140-6736(97)10301-4.
60.• Hilario A, Ramos A, Millan JM, Salvador E, Gomez PA, Cicuendez M, et al. Severe traumatic head injury: prognostic value of brain stem injuries detected at MRI. AJNR Am J Neuroradiol. 2012;33(10):1925–31. https://doi.org/10.3174/ajnr.A3092 **One hundred and eight patients with severe TBI were studied by magnetic resonance imaging in the first 30 days after trauma. Brain stem injury was categorized as anterior or posterior, hemorrhagic or non-hemorrhagic, and unilateral or bilateral. Outcome measures were GOSE and Barthel Index 6 months post-injury. Posterior and bilateral brain stem injuries detected at magnetic resonance imaging are poor prognostic signs. Non-hemorrhagic injuries showed the highest positive predictive value for good outcome.**
61. Firsching R, Woischneck D, Klein S, Reissberg S, Döhring W, Peters B. Classification of severe head injury based on magnetic resonance imaging. Acta Neurochir. 2001;143(3):263–71. https://doi.org/10.1007/s007010170106.
62. Wedekind C, Hesselmann V, Lippert-Grüner M, Ebel M. Trauma to the pontomesencephalic brainstem-a major clue to the prognosis of severe traumatic brain injury. Br J Neurosurg. 2002;16(3):256–60. https://doi.org/10.1080/02688690220148842.
63. Weiss N, Galanaud D, Carpentier A, Tezenas de Montcel S, Naccache L, Coriat P, et al. A combined clinical and MRI approach for outcome assessment of traumatic head injured comatose patients. J Neurol. 2008;255(2):217–23. https://doi.org/10.1007/s00415-008-0658-4.
64.• Shakir A, Aksoy D, Mlynash M, Harris OA, Albers GW, Hirsch KG. Prognostic value of quantitative diffusion-weighted mri in patients with traumatic brain injury. J Neuroimaging. 2016;26(1):103–8. https://doi.org/10.1111/jon.12286 **Retrospective observational study investigated patients with moderate-to-severe TBI. MRIs obtained post-injury days 1–13 were analyzed. A good outcome was defined as discharge to home or a rehabilitation facility. Quantitative MRI offers additional prognostic information in acute TBI. A whole brain tissue ADC threshold of $< 400 \times 10^{-6}$ mm^2/s in $\geq 0.49\%$ of brain may be a novel prognostic biomarker.**
65. Tollard E, Galanaud D, Perlbarg V, Sanchez-Pena P, Le Fur Y, Abdennour L, et al. Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: preliminary results. Crit Care Med. 2009;37(4):1448–55. https://doi.org/10.1097/CCM.0b013e31819cf050.
66. Katz D. Neuropathology and neurobehavioral recovery from closed head injury. J Head Trauma Rehabil. 1992;72(2):1–15. https://doi.org/10.1097/00001199-200501000-00008.
67.•• Katz DI, Alexander MP. Traumatic brain injury. Predicting course of recovery and outcome for patients admitted to rehabilitation. Arch Neurol. 1994;51(7):661–70. https://doi.org/10.1001/archneur.1994.00540190041013 **The aim of this study was to demonstrate that the prognosis for patients with TBI using a consecutive sample of 243 patients admitted to a rehabilitation unit (age range, 8 through 89 years). Prolonged length of coma portends a worse outcome following severe TBI with a length of coma greater than 4 weeks making good recovery unlikely while severe disability is unlikely when duration of coma is less than 2 weeks. The longer the duration of PTA the worse the patient outcome with severe disability unlikely when PTA is less than 2 months, though good recovery is unlikely when duration of PTA is greater than 3 months.**
68. M-STFo PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med. 1994;330(21):1499–508. https://doi.org/10.1056/NEJM199405263302107.
69. Katz DI, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1-4 year follow-up. Prog Brain Res. 2009;177:73–88. https://doi.org/10.1016/S0079-6123(09)17707-5.
70. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53. https://doi.org/10.1212/wnl.58.3.349.
71. Levin HS, O'Donnell VM, Grossman RG. The Galveston Orientation and Amnesia Test. A practical scale to assess cognition after head injury. J Nerv Ment Dis. 1979;167(11):675–84. https://doi.org/10.1097/00005053-197911000-00004.
72. Wade DT. Measurement in neurological rehabilitation. Curr Opin Neurol Neurosurg. 1992;5(5):682–6.
73. Zafonte RD, Mann NR, Millis SR, Black KL, Wood DL, Hammond F. Posttraumatic amnesia: its relation to functional outcome. Arch Phys Med Rehabil. 1997;78(10):1103–6. https://doi.org/10.1016/s0003-9993(97)90135-0.
74. Novack TA, Dowler RN, Bush BA, Glen T, Schneider JJ. Validity of the orientation log, relative to the Galveston Orientation and Amnesia Test. J Head Trauma Rehabil. 2000;15(3):957–61. https://doi.org/10.1097/00001199-200006000-00008.
75.•• Walker WC, Ketchum JM, Marwitz JH, Chen T, Hammond F, Sherer M, et al. A multicentre study on the clinical utility of post-traumatic amnesia duration in predicting global outcome after moderate-severe traumatic brain injury. J Neurol Neurosurg Psychiatry. 2010;81(1):87–9. https://doi.org/10.1136/jnnp.2008.161570 **Study assessed the relationship between PTA duration and probability thresholds for GOS levels. Data were prospectively collected in this multicenter observational study. The cohort was a consecutive sample of rehabilitation patients enrolled in the National Institute on Disability and Rehabilitation Research funded TBI Model Systems (n = 1332) that had documented finite PTA duration greater than 24 h, and 1-year and 2-year GOS. Longer PTA resulted in an incremental decline in probability of good recovery and a corresponding increase in probability of severe disability. When PTA ended within 4 weeks, severe disability was unlikely (< 15% chance) at year 1, and good recovery was the most likely GOS at year 2. When PTA lasted beyond 8 weeks, good recovery was highly unlikely (< 10% chance) at year 1, and severe disability was equal to or more likely than moderate disability at year 2.**
76. Walker WC, Stromberg KA, Marwitz JH, Sima AP, Agyemang AA, Graham KM, et al. Predicting long-term global outcome after traumatic brain injury: development of a practical prognostic tool using the traumatic brain injury model systems national database. J Neurotrauma. 2018;35(14):1587–95. https://doi.org/10.1089/neu.2017.5359.
77. Kosty JA, Stein SC. Measuring outcome after severe TBI. Neurol Res. 2013;35(3):277–84. https://doi.org/10.1179/1743132813Y.0000000168.
78. Wilde EA, Whiteneck GG, Bogner J, Bushnik T, Cifu DX, Dikmen S, et al. Recommendations for the use of common outcome measures in traumatic brain injury research. Arch Phys Med Rehabil. 2010;91(11):1650–60.e17. https://doi.org/10.1016/j.apmr.2010.06.033.
79. Maas AI, Harrison-Felix CL, Menon D, Adelson PD, Balkin T, Bullock R, et al. Common data elements for traumatic brain injury: recommendations from the interagency working group on

demographics and clinical assessment. Arch Phys Med Rehabil. 2010;91(11):1641–9. https://doi.org/10.1016/j.apmr.2010.07.232.

80. Zelnick LR, Morrison LJ, Devlin SM, Bulger EM, Brasel KJ, Sheehan K, et al. Addressing the challenges of obtaining functional outcomes in traumatic brain injury research: missing data patterns, timing of follow-up, and three prognostic models. J Neurotrauma. 2014;31(11):1029–38. https://doi.org/10.1089/neu.2013.3122.
81. Forslund MV, Perrin PB, Røe C, Sigurdardottir S, Hellstrøm T, Berntsen SA, et al. Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury. Front Neurol. 2019;10. https://doi.org/10.3389/fneur.2019.00219.
82.• Quach NT, Ehsanian R, Dirlikov B, Sechrist S, Mohole J, McKenna S, et al. Burden of care implications and association of intracranial hypertension with extremely severe post-traumatic amnesia after traumatic brain injury: a 5-year retrospective longitudinal study. Front Neurol. 2019;10. https://doi.org/10.3389/fneur.2019.00034 **Study aimed to evaluate the burden of care in individuals with extremely severe PTA (esPTA; PTA > 28 days) from acute inpatient rehabilitation admission to 5 years post-injury as well as the association between intracranial hypertension (ICH; intracranial pressure (ICP) ≥ 20 mmHg) and esPTA status. Three hundred and forty-two individuals with moderate-to-severe TBI enrolled in the Northern California TBI Model System (TBIMS) of Care. Individuals with esPTA have increased short- and long-term burden of care and the presence of ICH during hospitalization increased the odds of experiencing esPTA.**
83. The FIM Instrument: its background, structure, and usefulness. Buffalo, NY: UDSMR: Uniform Data System for Medical Rehabilitation. 2012. https://www.file:///C:/Users/j1w6en/Downloads/the-fim-instrument-its-background-structure-and-usefulness.pdf.
84. Hamilton BB, Deutsch A, Russell C, Fiedler RC, Granger CV. Relation of disability costs to function: spinal cord injury. Arch Phys Med Rehabil. 1999;80(4):385–91. https://doi.org/10.1016/s0003-9993(99)90274-5.
85.• Spitz G, Mahmooei BH, Ross P, McKenzie D, Ponsford JL. Characterizing early and late return to work after traumatic brain injury. J Neurotrauma. 2019;36(17):2533–40. https://doi.org/10.1089/neu.2018.5850 **This study modelled early (within 6 months) and late (7–34 months) return to work by evaluating a large and comprehensive compensation database. The sample comprised 666 participants with TBI, the majority of whom sustained a moderate or severe injury caused by a motor vehicle accident. Early return to work was more likely for individuals who were pre-morbidly employed in a managerial or professional occupation and those who experienced shorter post-traumatic amnesia. Return to work was less likely in the late phase for individuals who were older, experienced longer post-traumatic amnesia, had an abdominal injury, and used more specialist practitioners.**
86. Howe EI, Andelic N, Perrin PB, Røe C, Sigurdardottir S, Arango-Lasprilla JC, et al. Employment probability trajectories up to 10 years after moderate-to-severe traumatic brain injury. Front Neurol. 2018;9. https://doi.org/10.3389/fneur.2018.01051.
87. Königs M, de Kieviet JF, Oosterlaan J. Post-traumatic amnesia predicts intelligence impairment following traumatic brain injury: a meta-analysis. J Neurol Neurosurg Psychiatry. 2012;83(11):1048–55. https://doi.org/10.1136/jnnp-2012-302635.
88. McDonald CM, Jaffe KM, Fay GC, Polissar NL, Martin KM, Liao S, et al. Comparison of indices of traumatic brain injury severity as predictors of neurobehavioral outcome in children. Arch Phys Med Rehabil. 1994;75(3):328–37. https://doi.org/10.1016/0003-9993(94)90038-8.
89. Knights RM, Ivan LP, Ventureyra EC, Bentivoglio C, Stoddart C, Winogron W, et al. The effects of head injury in children on neuropsychological and behavioural functioning. Brain Inj. 1991;5(4):339–51. https://doi.org/10.3109/02699059109008107.
90. Perrin PB, Niemeier JP, Mougeot JL, Vannoy CH, Hirsch MA, Watts JA, et al. Measures of injury severity and prediction of acute traumatic brain injury outcomes. J Head Trauma Rehabil. 2015;30(2):136–42. https://doi.org/10.1097/HTR.0000000000000026.
91. Sichez JP, Sichez N, Bitar A, Melon E. Functional prognosis in skull injuries with signs of axial damage. Value of the quality of the arousal phase (series of 80 cases). Neurochirurgie. 1983;29(1):21–3.
92. Eastvold AD, Walker WC, Curtiss G, Schwab K, Vanderploeg RD. The differential contributions of posttraumatic amnesia duration and time since injury in prediction of functional outcomes following moderate-to-severe traumatic brain injury. J Head Trauma Rehabil. 2013;28(1):48–58. https://doi.org/10.1097/HTR.0b013e31823c9317.
93. Sherer M, Stouter J, Hart T, Nakase-Richardson R, Olivier J, Manning E, et al. Computed tomography findings and early cognitive outcome after traumatic brain injury. Brain Inj. 2006;20(10):997–1005. https://doi.org/10.1080/02699050600677055.
94. Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. J Neurotrauma. 2004;21(11):1553–61. https://doi.org/10.1089/neu.2004.21.1553.
95. Raabe A, Grolms C, Seifert V. Serum markers of brain damage and outcome prediction in patients after severe head injury. Br J Neurosurg. 1999;13(1):56–9. https://doi.org/10.1080/02688699944195.
96. Raabe A, Grolms C, Sorge O, Zimmermann M, Seifert V. Serum S-100B protein in severe head injury. Neurosurgery. 1999;45(3):477–83. https://doi.org/10.1097/00006123-199909000-00012.
97. Vos PE, Lamers KJ, Hendriks JC, van Haaren M, Beems T, Zimmerman C, et al. Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. Neurology. 2004;62(8):1303–10. https://doi.org/10.1212/01.wnl.0000120550.00643.dc.
98. Vos PE, Jacobs B, Andriessen TM, Lamers KJ, Borm GF, Beems T, et al. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology. 2010;75(20):1786–93. https://doi.org/10.1212/WNL.0b013e3181fd62d2.
99. Pelinka LE, Toegel E, Mauritz W, Redl H. Serum S 100 B: a marker of brain damage in traumatic brain injury with and without multiple trauma. Shock. 2003;19(3):195–200. https://doi.org/10.1097/00024382-200303000-00001.
100. Elting JW, de Jager AE, Teelken AW, Schaaf MJ, Maurits NM, van der Naalt J, et al. Comparison of serum S-100 protein levels following stroke and traumatic brain injury. J Neurol Sci. 2000;181(1–2):104–10. https://doi.org/10.1016/s0022-510x(00)00442-1.
101. Böhmer AE, Oses JP, Schmidt AP, Perón CS, Krebs CL, Oppitz PP, et al. Neuron-specific enolase, S100B, and glial fibrillary acidic protein levels as outcome predictors in patients with severe traumatic brain injury. Neurosurgery. 2011;68(6):1624–30; discussion 30-1. https://doi.org/10.1227/NEU.0b013e318214a81f.
102. Rainey T, Lesko M, Sacho R, Lecky F, Childs C. Predicting outcome after severe traumatic brain injury using the serum S100B biomarker: results using a single (24h) time-point. Resuscitation. 2009;80(3):341–5. https://doi.org/10.1016/j.resuscitation.2008.
103. Goyal A, Failla MD, Niyonkuru C, Amin K, Fabio A, Berger RP, et al. S100b as a prognostic biomarker in outcome prediction for patients with severe traumatic brain injury. J Neurotrauma. 2013;30(11):946–57. https://doi.org/10.1089/neu.2012.2579.
104. Lumpkins KM, Bochicchio GV, Keledjian K, Simard JM, McCunn M, Scalea T. Glial fibrillary acidic protein is highly correlated with brain injury. J Trauma. 2008;65(4):778–82; discussion 82-4. https://doi.org/10.1097/TA.0b013e318185db2d.
105. Papa L, Akinyi L, Liu MC, Pineda JA, Tepas JJ, Oli MW, et al. Ubiquitin C-terminal hydrolase is a novel biomarker in humans for

severe traumatic brain injury. Crit Care Med. 2010;38(1):138–44. https://doi.org/10.1097/CCM.0b013e3181b788ab.

106. Brophy GM, Mondello S, Papa L, Robicsek SA, Gabrielli A, Tepas J, et al. Biokinetic analysis of ubiquitin C-terminal hydrolase-L1 (UCH-L1) in severe traumatic brain injury patient biofluids. J Neurotrauma. 2011;28(6):861–70. https://doi.org/10.1089/neu.2010.1564.

107.•• Frankel M, Fan L, Yeatts SD, Jeromin A, Vos PE, Wagner AK, et al. The association of very early serum levels of S100B, GFAP, UCH-L1, and SBDP with outcome in ProTECT III. J Neurotrauma. 2019. https://doi.org/10.1089/neu.2018.5809 **This study (BIO-ProTECT) tested the hypothesis that serum biomarkers of structural brain injury, collected within 4 h after injury, add value when predicting unfavorable outcome 6 months after moderate-to-severe acute TBI. Compared with a model containing baseline patient variables/characteristics, inclusion of αII-spectrin breakdown product of molecular weight 150 (S100B) and GFAP (but not UCH-L1 and SBDP) significantly improved prognostic capability. A combined predictive model incorporating baseline patient characteristics and biomarker data (S100B and GFAP) had the best prognostic capability.**

108. Judson JA, Cant BR, Shaw NA. Early prediction of outcome from cerebral trauma by somatosensory evoked potentials. Crit Care Med. 1990;18(4):363–8. https://doi.org/10.1097/00003246-199004000-00003.

109. Hume AL, Cant BR, Shaw NA. Central somatosensory conduction time in comatose patients. Ann Neurol. 1979;5(4):379–84. https://doi.org/10.1002/ana.410050412.

110. Hume AL, Cant BR. Central somatosensory conduction after head injury. Ann Neurol. 1981;10(5):411–9. https://doi.org/10.1002/ana.410100503.

111. Moulton RJ, Shedden PM, Tucker WS, Muller PJ. Somatosensory evoked potential monitoring following severe closed head injury. Clin Invest Med. 1994;17(3):187–95.

112. Pohlmann-Eden B, Dingethal K, Bender HJ, Koelfen W. How reliable is the predictive value of SEP (somatosensory evoked potentials) patterns in severe brain damage with special regard to the bilateral loss of cortical responses? Intensive Care Med. 1997;23(3):301–8. https://doi.org/10.1007/s001340050332.

113. Sleigh JW, Havill JH, Frith R, Kersel D, Marsh N, Ulyatt D. Somatosensory evoked potentials in severe traumatic brain injury: a blinded study. J Neurosurg. 1999;91(4):577–80. https://doi.org/10.3171/jns.1999.91.4.0577.

114. Morgalla MH, Bauer J, Ritz R, Tatagiba M. Coma. The prognostic value of evoked potentials in patients after traumatic brain injury. Anaesthesist. 2006;55(7):760–8. https://doi.org/10.1007/s00101-006-1036-1.

115. Amantini A, Grippo A, Fossi S, Cesaretti C, Piccioli A, Peris A, et al. Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. Clin Neurophysiol. 2005;116(1):229–35. https://doi.org/10.1016/j.clinph.2004.07.008.

116. Schorl M, Valerius-Kukula SJ, Kemmer TP. Median-evoked somatosensory potentials in severe brain injury: does initial loss of cortical potentials exclude recovery? Clin Neurol Neurosurg. 2014;123:25–33. https://doi.org/10.1016/j.clineuro.2014.05.004.

117. González-García E, Vilela-Soler C, Romá-Ambrosio J, Fenollosa-Entrena B. The use of evoked potentials in the follow-up and prognosis of patients in coma following severe traumatic brain injury. Rev Neurol. 2007;44(7):404–10. https://doi.org/10.33588/rn.4407.2006225.

118. Rollnik JD. Clinical neurophysiology of neurologic rehabilitation. Handb Clin Neurol. 2019;161:187–94. https://doi.org/10.1016/B978-0-444-64142-7.00048-5.

119. Morgalla MH, Tatagiba M. Long-term outcome prediction after a traumatic brain injury using early somatosensory and acoustic evoked potentials: analysis of the predictive value of the different single components of the potentials. Neurodiagn J. 2014;54(4):338–52. https://doi.org/10.1080/21646821.2014.11106818.

120. Popernack ML, Gray N, Reuter-Rice K. Moderate-to-severe traumatic brain injury in children: complications and rehabilitation strategies. J Pediatr Health Care. 2015;29(3):e1–7. https://doi.org/10.1016/j.pedhc.2014.09.003.

121. McCarthy ML, MacKenzie EJ, Durbin DR, Aitken ME, Jaffe KM, Paidas CN, et al. Health-related quality of life during the first year after traumatic brain injury. Arch Pediatr Adolesc Med. 2006;160(3):252–60. https://doi.org/10.1001/archpedi.160.3.252.

122. Treble-Barna A, Zang H, Zhang N, Taylor HG, Yeates KO, Wade S. Long-term neuropsychological profiles and their role as mediators of adaptive functioning after traumatic brain injury in early childhood. J Neurotrauma. 2017;34(2):353–62. https://doi.org/10.1089/neu.2016.4476.

123. Catroppa C, Anderson VA, Morse SA, Haritou F, Rosenfeld JV. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury (TBI). J Pediatr Psychol. 2008;33(7):707–18. https://doi.org/10.1093/jpepsy/jsn006.

124. Davis C, Slomine S, Salorio F, Suskauer J. Time to follow commands and duration of post-traumatic amnesia predict GOS-E PEDS scores 1–2 years after TBI in children requiring inpatient rehabilitation. J Head Trauma Rehabil. 2016;31(2):E39–47. https://doi.org/10.1097/HTR.0000000000000159.

125. Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, et al. Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. J Neurosurg Pediatr. 2015;16(4):410–9. https://doi.org/10.3171/2015.3.PEDS14679.

126. Briggs R, Brookes N, Tate R, Lah S. Duration of post-traumatic amnesia as a predictor of functional outcome in school-age children: a systematic review. Dev Med Child Neurol. 2015;57(7):618–27. https://doi.org/10.1111/dmcn.12674.

127. Suskauer SJ, Slomine BS, Inscore AB, Lewelt AJ, Kirk JW, Salorio CF. Injury severity variables as predictors of WeeFIM scores in pediatric TBI: time to follow commands is best. J Pediatr Rehabil Med. 2009;2(4):297–307.

128. Austin CA, Slomine BS, Dematt EJ, Salorio CF, Suskauer SJ. Time to follow commands remains the most useful injury severity variable for predicting WeeFIM® scores 1 year after paediatric TBI. Brain Inj. 2013;27(9):1056–62. https://doi.org/10.3109/02699052.2013.794964.

129. Crowe LM, Catroppa C, Babl FE, Anderson V. Intellectual, behavioral, and social outcomes of accidental traumatic brain injury in early childhood. Pediatrics. 2012;129(2):e262–8. https://doi.org/10.1542/peds.2011-0438.

130. Ewing-Cobbs L, Prasad MR, Kramer L, Cox CS, Baumgartner J, Fletcher S, et al. Late intellectual and academic outcomes following traumatic brain injury sustained during early childhood. J Neurosurg. 2006;105(4 Suppl):287–96. https://doi.org/10.3171/ped.2006.105.4.287.

131. Smitherman E, Hernandez A, Stavinoha PL, Huang R, Kernie SG, Diaz-Arrastia R, et al. Predicting outcome after pediatric traumatic brain injury by early magnetic resonance imaging lesion location and volume. J Neurotrauma. 2016;33(1):35–48. https://doi.org/10.1089/neu.2014.3801.

132. Grados MA, Slomine BS, Gerring JP, Vasa R, Bryan N, Denckla MB. Depth of lesion model in children and adolescents with moderate to severe traumatic brain injury: use of SPGR MRI to predict severity and outcome. J Neurol Neurosurg Psychiatry. 2001;70(3):350–8. https://doi.org/10.1136/jnnp.70.3.350.