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REVIEW

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Baseline Predictors of Survival, Neurological Recovery, Cognitive Function, Neuropsychiatric Outcomes, and Return to Work in Patients after a Severe Traumatic Brain Injury: an Updated Review

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ABSTRACT

Introduction: Severe traumatic brain injury (sTBI) is a common cause of death and disability worldwide, with long-term sequelae among survivors that include cognitive deficits, psychosocial and neuropsychiatric dysfunction, failure to return to pre-injury levels of work, school and inter-personal relationships, and overall reduced quality of and satisfaction with life. **Aim:** The aim of this work is to review the current literature on baseline predictors of outcomes in adults post sTBI. **Method:** Most of available literature on baseline predictors of outcomes in adults post sTBI were reviewed and summarized in this work. **Results:** Currently, a sizeable number of composite predictors of mortality and overall function exists; however, these instruments tend to over-estimate poor outcomes and fail to address issues like cognition, psychosocial/neuropsychiatric dysfunction, and return to work or school. **Conclusion:** This article reviews currently-identified predictors of all these outcomes.

Keywords: Severe traumatic brain injury, predictor, IMPACT, CRASH, outcomes, cognitive outcomes, neuropsychiatric outcomes, return to work.

1. INTRODUCTION

Severe traumatic brain injury (sTBI) is a common cause of death and disability worldwide (1-4), with 14- and 30-day mortality rates

frequently in the 15-30% range (2, 5-8). On the other hand, up to half of patients experience significant recovery, to the point where they become able to take care of themselves, and perhaps even return to work or school (9). For obvious reasons, physicians treating patients with sTBI often are called to predict their patient's prognosis, and not just with respect to survival, so that it can be used for treatment decisions, the allocation of resources, and communications with loved ones and other caregivers (10, 11). Questions like 'will the patient regain consciousness', 'will the patient be permanently disabled and, if so, to what degree' and 'will the patient be able to return to school or work' abound.

Traditionally, the Glasgow Coma Scale (GCS) has been used by clinicians to predict the likelihood of patient survival and recovery. More recently, various composite instruments - like the Trauma and Injury Severity Score (TRISS), Corticosteroid Randomization After Significant Head Injury (CRASH), and International Mission for Prognosis and Analysis of Clinical Trials in TBI (TBI-IMPACT) - have been developed and validated (12). Such instruments tend to over-estimate rates of mortality and severe disability, however, and fail to address such potential outcomes like time to consciousness, overall cognitive function, and return to work or school.

They also were largely developed and validated in hybrid populations that incorporated patients with both moderate and severe TBI (13).

Since its first reporting in 1975, by Jennett and Bond, the Glasgow Outcome Scale (GOS) has been used as a means to rank outcomes in patients with brain injury. As listed in Table 1, each patient's recovery is categorized according to five levels: death; persistent vegetative state; severe disability requiring care; moderate disability; and mild disability. In research, the GOS is often dichotomized, characterizing patients as having experienced either a poor outcome, as GOS levels 1-3; or a good outcome, with a GOS score of 4 or 5 (14, 15). In general, assessments of outcome predictors have focused on the negative outcomes of mortality and low GOS score, particularly within the first six to 12 months after the injurious event (16).

The current paper is a review of the current literature on baseline predictors of outcomes in adults post sTBI. Unlike almost all prior reviews, however, it extends beyond just mortality and GOS score to address other outcomes. These include the likelihood of and time to consciousness, various components of cognitive recovery, neuropsychiatric complications, and the patient's capacity to ultimately return to work or school.

2. BASELINE PREDICTORS OF MORTALITY AND GLASGOW OUTCOME SCORE

Predicting mortality and the GOS has been the primary role of the various outcome-predictor instruments that have been developed over the years, and the major function for which they have been tested (5, 12, 13, 17-23).

The tool which has been used the longest, and which still is used both singly and as a component of composite scores, is the Glasgow Coma Scale (GCS), a scale that rates patients in terms of their motor function, eye function, and speech, each rated from a low of 1 to a high of 4, 5 or 6, depending on the function being measured, so that the final score ranges from 3 (fully vegetative) to 15 (fully conscious). Combined with information on a patient's pupils' reactivity to light, the GCS remains the most-commonly utilized prognostic tool in clinical practice, the combination of a GCS of 3 and bilaterally fixed, dilated pupils portending in-house mortality rates between 80 and 100% (18, 22, 24). The GCS tends to over-estimate mortality and severe disability, however, as shown in a recently-published study in which, among 189 patients presenting with a GCS of 3, 50.7% survived, and roughly one in seven ultimately achieved a good outcome; this included one patient who presented with a GCS of 3 and bilaterally fixed and dilated pupils (18). The GCS, with or without pupillary reactivity, also fails to take into consideration the significant role that patient age seems to play in determining outcomes post sTBI (5, 25-27), as well as other factors like the patient's other injuries, general health status, current consumption of drugs and/or alcohol, and findings on imaging (28).

Of the various composite instruments that have been developed, the IMPACT (29, 30) and CRASH (31) composite scores are the most frequently used, both in research and clinically, having been developed on the largest cohorts of any models (involving 8509 and 10,008 patients, respec-

tively) and most often externally validated (between them, in 91 studies) (32). This said, other models have also been developed and validated, including a Brazilian model (27) and a Dutch model initially tested in the city of Nijmegen (33). All these models, and most others, share the three previously-mentioned predictors—GCS, pupillary reactivity, and age—though the IMPACT model only utilizes the motor component of the GCS (Table 2).

The IMPACT and CRASH tools both have core and extended versions, the CRASH adding computed tomography (34) findings, when available, and the IMPACT having two extended versions, one including hypoxemia, hypotension and CT findings; the other also adding serum glucose and hemoglobin levels. Both the IMPACT and CRASH tools have on-line calculators (35, 36). Several studies have compared these prognostic tools and found them to be roughly equivalent in their ability to predict mortality and poor outcomes. For example, in one study involving 635 Japanese patients with TBI entered into the Japan Neurotrauma Data Bank, the TBI-IMPACT and CRASH instruments were compared against a generic-injury predictor called the Trauma and Injury Severity Score (TRISS), though all three instruments predicted mortality, for unfavorable outcomes at 6 months, the CRASH (basic and computed tomography) and IMPACT (core and core extended) models had area under the curve values (0.86 and 0.86; 0.81 and 0.85, respectively) that were both similar and superior to that achieved with the TRISS model (0.75) (12). And in a meta-analysis assessing 67 different prognostic models for functional outcome after TBI in patients age ≥ 14 years with a Glasgow Coma Scale (GCS) score ≤ 12 published between 2006-2018, the three most common predictors identified were the GCS (motor) score ($n=55$), age ($n=54$), and pupillary reactivity ($n=48$), the core components of the IMPACT instrument; and both the IMPACT and CRASH models yielded AUCs ranging between 0.65-0.90 and 0.66-1.00, respectively (32). Despite this, both the IMPACT and CRASH instruments, as well as other predictive models, have been demonstrated to often over-estimate the rate of both adverse outcomes (17, 19, 21, 37, 38).

Numerous studies have documented the predictive power of computed tomography (34) findings, such that they have now been integrated into the extended versions of both the IMPACT and the CRASH prognostic tools (35, 36) (Table 2). Among the various CT findings that have been individually identified as predictors of mortality and poor outcome in sTBI patients are the presence of traumatic subarachnoid hemorrhage (27, 39, 40), intra-ventricular hemorrhage (39, 40), obliteration of the cisterns (39, 40), midline shift (40), epidural hemorrhage (39), and mass lesions (40). Several models have been developed for use assessing CT findings in patients with traumatic brain injuries, all slightly different. Among others, they include the Marshall (41), Rotterdam (42), Stockholm (43), Shanghai (11), and Helsinki (44) classification systems. Of these, the most commonly used is the Marshall system, which remains the "gold standard", largely because it was the developed first, in 1991 (41). It divides TBI into diffuse versus focal lesions, differentiating within these categories by taking into account basal cistern compression and midline shift

1. Death	Severe injury or death without recovery of consciousness
2. Persistent vegetative state	Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions
3. Severe disability	Severe injury with permanent need for help with daily living
4. Moderate disability	No need for assistance in everyday life; employment possible, but may require special equipment
5. Low disability	Light damage with minor neurological and psychological deficits

Table 1. Glasgow Outcome Scale

with diffuse lesions, and by considering the volume with focal lesions (41). To date, however, few comparisons of the various systems have been done, and the relative accuracies of the different approaches remain unclear.

Because of its ability to yield more accurate information on the extent of diffuse injuries and the absence of radiation, magnetic resonance imaging (MRI) might also have a role as a predictor of survival in patients with sTBI. However, its widespread application is restricted by cost, its limited availability at many centers, and the difficulties that are inherent using it in patients who are physiologically unstable (45). Its role in sTBI patients is still being evaluated (46).

Among baseline laboratories, one which specifically predicts mortality is an elevated ratio of neutrophils to lymphocytes in peripheral blood. This marker of inflammation has been found to be highly predictive of 28-day mortality post sTBI (47). Similarly, elevated serum lactate levels have been documented to be independently predictive of mortality and a poor outcome in both children and adults post sTBI (48, 49). Serum glucose and hemoglobin levels and the results of oximetry have been integrated into the extended version of the IMPACT tool (35).

Certain baseline predictors are still only being assessed experimentally and are not yet available for clinical practice. In one study involving 34 patients with sTBI (admission GCS score \leq 8), levels of tau protein (a protein that is almost ubiquitous in neural tissue) were found to be higher in the poor outcome group (436.2 \pm 473.6 pg/mL) than in the good outcome group (51.6 \pm 81.5 pg/mL) ($p < 0.0001$) (50). On univariate analysis, a low GCS score ($p = 0.001$), higher serum tau protein levels ($p < 0.001$), abnormal pupil light reflex ($p = 0.013$), and basal cistern compression on CT ($p = 0.026$) were all associated with a poor outcome, with the GCS score and tau protein level still significant predictors on multivariate analysis. In another multicenter, observational, prospective study involving 124 sTBI patients with a baseline GCS score \leq 9, non-survivors ($n = 34$) had greater serum substance P levels than their surviving counterparts on hospital days 1 ($p < 0.001$), 4 ($p < 0.001$), and 8 ($p < 0.001$) of TBI (51). The areas under the serum substance P concentration curve were 76% ($P < 0.001$), 87% ($P < 0.001$), and 89% ($P < 0.001$) for predicting 30-day mortality for the three data collection points, respectively.

Among those patients whose GCS appears to be improving over time, other predictors beyond baseline factors

appear to come into play. In one Italian study involving 43 patients who remained comatose 15 days post sTBI, the time to first oral feeding was the factor that best predicted one-year GOS score, followed by the time to optical fixation, time to ability to follow commands, and time to spontaneous motor activity (52).

3. PREDICTORS OF TIME TO CONSCIOUSNESS

Among loved ones, one of the most pressing questions, especially during the acute phase post injury, pertains to if and when the patient is going to regain consciousness.

In one interesting study, rather than identifying predictors of mortality and long-term poor outcomes, Wilans et al specifically sought to identify predictors of (a) a return to consciousness (defined as following verbal commands); and (b) the time that would elapse before a return to consciousness (26). Among 402 post-sTBI comatose adults who presented over a seven-year span, from 2010 through 2017, whether patients regained consciousness or not was inversely associated with the patient's age (with younger patients more likely to regain consciousness), as well as with the injury severity score (ISS) and Rotterdam score of CT findings (lower scores associated with an increased likelihood of regaining consciousness), and the presence of at least one fixed, dilated pupil (associated with a decreased likelihood of regaining consciousness). The time required for the patient to return to consciousness was inversely correlated with the same four predictors.

4. PREDICTORS OF COGNITIVE RECOVERY

Numerous studies have shown that patients who survive a sTBI often are left with cognitive, psychosocial and neuropsychiatric difficulties that can persist for years, and sometimes decades (53–58). In one study in which 86 patients with sTBI were assessed in face-to-face interviews an average of eight years post-injury, problems with memory, slowness and problems with concentration were reported by 71%, 68% and 67% of the sample, respectively (59). Moreover, cognitive problems were significantly more frequent than physical symptoms, among which difficulties with balance (47.5%), headaches (36.0%) and problems with mortality (31.0%) were most common (59).

Specific areas of cognition that appear to be characteristically involved are processing speed (34, 60, 61), attention (62–64), executive functioning (60, 63, 65), and learning and memory (60, 66, 67). In addition to other factors that are predictive, certain baseline factors appear to predict virtually all the above-listed cognitive components; these are the patient's age, the patient's estimated pre-injury level of intelligence, the duration of post-traumatic amnesia, and the severity of injury.

In longitudinal studies, younger age has been documented to predict both enhanced processing speed 12 months post injury and increased rate of processing speed recovery in patients who have suffered a sTBI; a higher estimated pre-injury intelligence quotient (IQ) similarly was found to be associated with enhanced 12-month processing speed (61, 68). The same two factors - younger age and a higher estimated baseline intelligence, indicated by either pre-injury IQ or pre-injury years of education - have been linked

to enhanced performance on the Paced Auditory Serial Addition Task (PASAT), a measure of sustained attention one year post sTBI (69); to augmented performance on untimed executive tasks (68); to stabilization or recovery of, versus decline in, memory over time (70); and to enhanced visual and verbal memory (68, 71), all 12 months post sTBI. These effects seem to persist beyond 12 months, as well. In one study published in 2015, by Finnanger et al (63), in which 67 adolescents and adults with moderate-to-severe TBI between two and five years post injury were compared against 72 matched, healthy controls, fewer years of education and symptoms of depression were associated with greater executive dysfunction, while younger age at injury and depressive symptoms predicted greater executive dysfunction, and age at injury more aggressive and rule-breaking behaviors. In another, longitudinal study in which 182 patients with mild to severe TBI were followed for up to five years, Millis et al (56) discovered that each 10-year increase in age at the time of injury increased the risk of executive function impairment by almost 500%.

Comparing patients with moderate versus severe TBI, as determined by the baseline GCS, the latter have similarly been identified as having greater impairment in processing speed six months post injury (72); reduced performance on the PASAT three and five years post injury (53); and greater impairment in story and visual memory at six months, though this difference no longer was apparent two years out (72). Meanwhile, patients with longer periods of coma have been found to perform worse in a task of executive function called the Wisconsin Card Sorting Test (65).

Longer duration of post-traumatic amnesia (PTA) has likewise been linked to decreased processing speed (69); as well as to decreased executive functioning (affecting color-word interference, verbal fluency, and letter-digit sequencing) (60); impaired verbal memory (71); and an overall poor neurocognitive outcome (73).

Other predictors of reduced cognitive function that have been identified, at least in single studies, include patient gender. In one study of 1331 patients in which females and males were compared on the Wisconsin Card Sorting Test, females outperformed males even after multivariate adjustments for level of education and ethnicity (65). To date, differences between males and females have not been reported for processing speed, attention, or learning and memory. Other baseline factors that may predict long-term cognitive function after a sTBI include a pre-injury history of substance abuse (65) and findings of diffuse axonal injury detected during magnetic resonance imaging (MRI) of the brain(63). Interestingly, a violent cause of sTBI has also been found to predict a more than two-fold increase in the likelihood of executive dysfunction (65).

Model	Patient age	GCS	Pupil reactivity	Other
TBI-IMPACT-core	+	motor score	+	-
TBI-IMPACT-CT extended	+	motor score	+	hypotension, hypoxia, CT findings*
TBI-IMPACT-CT & lab extended	+	motor score	+	hypotension, hypoxia, CT findings*, serum glucose & Hgb
CRASH-core	+	+	+	extracranial injury
CRASH-extended	+	+	+	extracranial injury, CT findings**
Brazilian model	+	+	+	CT findings***
Dutch model (Nijmegen)	+	+	+	hypotension, CT findings

Table 2. Comparing outcome predictor models for TBI IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in TBI; CRASH = Corticosteroid Randomization After Significant Head Injury; CT = computed tomography; Hgb = hemoglobin; *CT findings in the extended IMPACT models = diffuse brain injury, evacuated vs... non-evacuated hemorrhage, traumatic subarachnoid hemorrhage, epidural mass; **CT findings in the extended CRASH model = midline shift, petechial hemorrhages, traumatic subarachnoid hemorrhage, obliteration of the 3rd ventricle or basal cisterns, non-evacuated hemorrhage; ***CT findings in the Brazilian model = Marshall classification

5. PREDICTORS OF PSYCHOSOCIAL AND NEURO-PSYCHIATRIC DYSFUNCTION

Psychosocial and neuropsychiatric dysfunction are common sequelae of sTBI. Psychiatric conditions that often follow sTBI include depression (74-78), anxiety disorders (77, 78), post-traumatic stress disorder (PTSD) (79, 80) and substance abuse (81). In addition, patients also experience declines in their mobility due to being unable to drive (82), decreased participation in activities outside the home (82), emotional instability (83, 84), and reduced communication skills (85), all of which may reduce the number and quality of their interpersonal relationships (78, 86), and in turn impair their psychosocial functioning, community involvement and overall satisfaction with and quality of life (87). Despite this, to date, relatively little research has been published on factors predicting psychosocial and neuropsychiatric outcomes in patients post sTBI.

As with virtually all other outcomes, a patient's age at injury and severity of injury both have been found to be predictive of psychosocial/neuropsychiatric outcomes in patients post sTBI. In one prospective study in which 103 patients were assessed up to five years after their TBI, depression was common, with 51% of the sample (n = 52) meeting or exceeding the CES-D (Center of Epidemiological Studies - Depression) threshold for clinical depression (74). In this sample, both age \geq 60 and initial disability status were predictive of current level of function and overall well-being. Patient age and injury severity have been identified as predictive of neuropsychiatric outcomes in other studies, as well (88, 89).

In one study of 283 adults with moderate-to-severe TBI followed prospectively for between three and five years, the three strongest predictors of long-term, post TBI depression were less than a high-school education, an unstable

work history prior to the injury, and a history of pre-injury alcohol abuse (76). In turn, in a large US study in which 4464 patients with moderate-to-severe TBI were assessed between one and 20 years post injury, 20% of the sample reported some level of TBI injury that preceded their most recent TBI; and such a history was predictive of post-injury substance abuse (81).

In another study of 53 patients who had suffered mild-to-severe TBI, the duration of post-traumatic amnesia was found to be the strongest predictor of psychosocial outcome, as rated by relatives (90). One study has been published documenting the possible impact of imaging findings on neuropsychiatric outcomes. In this study, in which a baseline MRI was obtained in 251 patients with sTBI within one month of their hospitalization, those with MRI findings consistent with diffuse axonal injury were found to be significantly more likely than those without to exhibit evidence of one or more psychiatric disorders, cognitive impairment, and a poor overall outcome (as indicated by the Glasgow Outcome Scale score) (73). The volume of diffuse axonal injury also was predictive of a poor neurocognitive outcome.

Resilience is a term that indicates an individual's ability to acclimatize to and accept change, and has repeatedly been raised as an important issue among patients who have sustained a TBI, particularly when severe (89, 91-93). In general, levels of resilience are lower among sTBI patients than in the general population (91). Higher baseline levels of resilience have been linked to a variety of favorable post sTBI outcomes, including reduced levels of anxiety and disability, reduced levels of psychological distress and greater life satisfaction (91, 92). However, predictors of post-sTBI resilience have also been studied. In one such study, in which 195 patients with moderate-to-severe TBI were followed for up to one year post injury, non-minority status and the absence of pre-injury substance abuse both were predictive of post-injury level of resilience, as measured using the validated Connor-Davidson Resilience Scale (92).

6. PREDICTORS OF RETURN TO WORK OR SCHOOL

Of all the specific functional outcomes, return to work has perhaps been the most heavily studied. Return to work or school is an outcome that is of importance to not only the individual and their loved ones, but to society as well (94). Overall, between one third and two thirds of all sTBI survivors will return to work or school, at some level (95-102). Of these, up to half will return to their former employment, while the remainder will enter some new line of work (103). Those seeking new work tend to be younger, single and less educated, to have suffered a more severe TBI, and to have behavioral problems (103). For many, the return to work will either be temporary or intermittent (104). Those returning to school typically will lag behind their uninjured peers (105).

Baseline predictors of return to work among those with moderate-to-severe TBI include male gender (95, 106, 107), younger age (96, 100, 106-109), being a non-minority ethnically (106, 107, 109), having a life partner (95, 106), having a higher level of education (97, 106, 107), employment sta-

tus at the time of injury (95, 98, 101, 106, 107), white collar work (101), higher annual earnings (107), shorter duration of coma (100), and less severe baseline injury (95, 96, 98, 100, 101, 108, 110). Pre-injury histories of substance and abuse and psychiatric illness have been found to predict post-injury unemployment (111).

In one longitudinal observational study in Norway in which 97 individuals with moderate-to-severe TBI were followed for up to 10 years post injury, from 2005 onward, and employment outcomes assessed at one, two, five, and 10 years, roughly 50% remained employed across all time points (95). Being male ($p=0.016$), in a partnered relationship at the time of injury ($p=0.002$), employed at the time of injury ($p<0.001$), and in a white-collar profession ($p=0.005$) all were associated with a higher likelihood of employment at all-time points, as was having a higher baseline GCS score ($p=0.006$). Moreover, whereas employment probabilities remained fairly stable over time among men, they trended downward for women. Meanwhile, while employment probabilities remained reasonably stable over time among those who had been employed at the time of injury, they trended upward over time among those unemployed when injured (95). Initial GCS score also was found to be predictive of return to school within one year post-injury in a US study of 309 16-year-olds, among whom only 20% had returned to school within one year (112).

In another study of 105 Norwegian patients with moderate-to-severe TBI followed for up to five years post injury, those who remained unemployed averaged roughly nine years older than those who achieved either stable or unstable employment (101). They also had a baseline GCS that was roughly 0.8 points lower, had post-traumatic amnesia an average of almost 4½ days longer, and were hospitalized an average of 21 days longer than their employed counterparts.

7. CONCLUSION

In addition to causing death and severe disabilities, severe traumatic brain injuries have been documented to be associated with numerous other adverse outcomes, like long-term difficulties with cognition, psychosocial and neuropsychiatric impairment, and failure to return to pre-injury levels of employment and school. Composite predictive tools - like the IMPACT and CRASH instruments that include a patient's age, initial Glasgow Coma Scale score, and degree of pupillary reactivity, plus/minus other factors - are useful, particularly for assessing mortality and global function, but tend to over-estimate the rate of poor outcomes, and fail to address issues important to patients and their loved ones, like cognition, psychosocial and neuropsychiatric status, and return to work or school. For these outcomes, the patient's age and initial level of injury consistently appear to play a part. However, other factors like their pre-injury psychiatric health, education and work history, also seem to impact outcomes. Continued research is necessary to better delineate which patients are going to do well, and which patients not so well in the long-term, among those who survive their initial injuries.

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