Prediction of clinical outcome in severe traumatic brain injury

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Clinical manifestations of severe TBI and their utility in predicting patient outcome
4. Statistical models for outcome prediction in severe TBI patients
5. Imaging strategies for outcome prediction in severe TBI patients
6. Biomarkers for outcome prediction in severe TBI patients
7. Conclusions
8. References

1. ABSTRACT

Traumatic brain injury (TBI) is the main cause of death and disability in adults worldwide. Early detection of TBI would be useful for evaluating and designing treatment strategies. Both single predictors from early clinical examination and multiple hospitalization variables/parameters can be used to determine the long-term prognosis of TBI. Predictive models like the IMPACT or CRASH prognosis calculator (based on large sample sizes) can predict mortality and unfavorable outcomes. Moreover, imaging techniques like MRI (Magnetic Resonance Imaging) can also predict consciousness recovery and mental recovery in severe TBI, while biomarkers associated with stress correlate with, and hence can be used to predict, severity and mortality. All predictors have limitations in clinical application. Further studies comparing different predictors and models are required to resolve limitations of current predictors.

2. INTRODUCTION

Traumatic brain injury (TBI) is a major health problem worldwide. It is estimated to affect approximately 10 million people every year and is the leading cause of death and disability among young adults in Western countries (1,2). It affects 1.5 million people each year in the United States alone, 52,000 of whom die in-hospital (3). Higher incidence and poorer outcomes have been recorded in racial minority groups than in non-Hispanic whites (4-6). African-Americans and Asians have a higher in-hospital mortality rate than non-Hispanic whites, following TBI (4). Many survivors of TBI have residual defects in cognitive, emotional and behavioral functioning. Behavioral changes are common in patients with moderate to severe TBI (7-9), which negatively affects everyday life, social and vocational reintegration, and the overall quality of life of these patients (10-12).

Hence, it is necessary to accurately predict the outcome of traumatic brain injury. A survey of Canadian intensivists, neurosurgeons and neurologists revealed that an accurate prognosis might be extremely helpful during the first 7 days following severe TBI (13). In another survey on the favorability of patient prognosis at 1 year following injury, approximately one-third respondents agreed, one-third were neutral, and the rest disagreed that it would be unfavorable (13). Hence, early prediction of TBI will be useful not only for designing currently available treatments, but also for assessing novel therapeutic strategies in future randomized controlled trials (RCTs) using outcome versus predicted outcome as end-points. In this review, we discuss recent findings on the clinical predictors of severe TBI prognosis.

3. CLINICAL MANIFESTATIONS OF SEVERE TBI AND THEIR UTILITY IN PREDICTING PATIENT OUTCOME

While determining the prognosis of TBI, some previous studies focused on the clinical
Prediction of severe traumatic brain injury

manifestations of injury. The somatosensory evoked potential (SEP), a parameter recorded and used for evaluating the abnormality of the somatosensory tract that extends from the peripheral nerve to the cerebral cortex, can be correlated with the outcome in severe TBI. Unilateral or bilateral absence of the cortical component of SEP is associated with a poor outcome (death or severe disability) (14). Early SEP grades at day three following TBI are indicators of information-processing speed, working memory and the ability to attend to tasks 1 year after TBI. These findings suggest early SEP has a predictive property in both short and long term outcome of TBI. Amongst patients diagnosed with severe TBI, SEP grades I and III can provide an accurate prognosis in more than 80% cases (15). In short and medium term prognosis, visual evoked potential, besides SEP, is also valuable for predicting survival of patients rendered comatose due to severe TBI (16).

In addition to SEP, the disability status and quantitative cerebral blood flow can also be used as single predictors. A greater disability is found to be associated with better psychological functioning, which although seems paradoxical, is observed among patients with anosognosia or poor awareness of psychological functioning 1 year after TBI (17). Early prediction within the first 6 to 12 h following severe TBI can be obtained from quantitative cerebral blood flow, a parameter which can predict the 6-month outcome (18), in accordance with previous findings that cerebral perfusion pressure (CPP) (<60 mm Hg) and intracranial hypertension (ICP) (>30 mm Hg) have great potential in the prognosis of neurological deterioration (19) (Figure 1). The association between ICP and mortality was confirmed in a study of 501 children under 16 years of age and diagnosed with TBI (20). This suggested that quantitative cerebral blood flow in the early stage of severe TBI, can be used as a single predictor to determine long-term survival outcome. Transcranial Doppler (TCD) ultrasonography, which is used to measure ICP and CPP, has been validated as a tool for predicting the 6-month outcome in patients. When performed within the first 24 h of severe TBI, it correlates significantly with ICP and CPP values (21).

Another outcome predictor at 3 and 6 months post-injury, is duration of the coma (22). Also, the duration of posttraumatic amnesia and time since injury can predict functional outcomes 1 year after moderate to severe TBI (23). When the intelligence coefficient of patients was examined using the Wechsler adult intelligence scale III, after severe TBI, cognitive deficits such as a slow processing speed were detected as the predominant symptom; this could be correlated with predictors such as the length of coma and posttraumatic amnesia (24).

Although single predictors are useful in the prognosis of severe TBI, performing a comprehensive analysis of multiple factors has been considered, since this may provide more information than a single predictor. In a retrospective study involving 846 cases of severe TBI (Glasgow coma scale (GCS) < or = 8), multiple parameters such as the GCS score, age, pupillary response and size, hypoxia, hyperthermia and high ICP were associated with outcome 1 year after severe TBI (25). The outcomes included good recovery, moderate disability, severe disability, vegetative status and death. A study involving 12 patients that underwent bilateral decompressive craniectomy predicted good outcomes in younger patients with better pupillary response and neurological status on admission, following similar categories as the former study (26). With regard to survival and functional recovery, factors such as a reduction in economic and social costs, prevention and early treatment of complications, and maintenance of homeostasis predict a good outcome (27). However, in predicting cognitive function, pupillary examination, Marshal CT Classification, GCS and serum glucose level were found to have limited capability in determining

![Figure 1. Quantitative cerebral blood flow within the first 6 and 12 hours after severe TBI, cerebral perfusion pressure (CPP) and intracranial hypertension predict outcome after severe TBI.](image-url)
outcome in severe TBI patients (GCS≤8) (28). Hence, multiple hospitalization variables may be valuable in predicting outcomes of long-term behavioral rehabilitation, but not cognitive function, in severe TBI patients. However, since studies comparing the predictive effects of single predictors versus multiple factors are rare, it is difficult to conclude which of the two is a better strategy in the prognosis of severe TBI.

4. STATISTICAL MODELS FOR OUTCOME PREDICTION IN SEVERE TBI PATIENTS

While multiple predictors may provide valuable information in the prognosis of severe TBI, predictive models based on a statistical model and large sample size, may be more accurate and practical. A comprehensive model that included multiple factors such as pre-injury behavioral problems, sex of the patient (male), post-injury cognitive and physical deficits and lack of access to transportation, predicted largely unfavorable occupational performance outcomes (29). Analysis of data from 513 severe closed head-injury patients using a hybrid model with baseline admission parameters could accurately predict the 6-month injury outcome (30). Another predictive model based on age, absence of light reflex, presence of extensive subarachnoid hemorrhage, intracranial pressure and midline shift, has a high predictive value in severe TBI (31).

The models mentioned above are limited by small sample size. The International Mission on Prognosis in Traumatic Brain Injury (IMPACT) project, which is focused on advancing knowledge in prognosis, trial-design and treatment of TBI, has been developed on a dataset obtained from 8509 patients from eleven studies on moderate and severe TBI (32). The IMPACT project developed three different models based on the dichotomized GOS (Glasgow outcome scale) at 6 months after injury: the Core Model, the Extended Model and the Lab Model, for the prediction of mortality and unfavorable outcome (including death, vegetative state and severe disability) (Figure 2). An external validation of the IMPACT models with a total of 9,036 moderate and severe TBI patients confirmed its generalizability in predicting mortality and unfavorable outcomes (33). Similar predictions were made using the Corticosteroid Randomisation after Significant Head Injury (CRASH) prognostic models (33). The IMPACT prognostic models were further validated in a study that included 508 patients diagnosed with moderate or severe TBI; the IMPACT models could reliably predict the probability of mortality and unfavorable outcome at 6 months after injury (34).

However, when the IMPACT and CRASH prognosis calculators were applied to severe TBI patients treated with an ICP-targeted therapy based on the Lund concept, both models led to an overestimation of mortality and unfavorable outcome (35,36). The Lund Concept is an approach used for treatment of severe brain trauma, and is mainly based on hypotheses originating from the physiology of brain volume and cerebral perfusion regulation (37,38). Moreover, a study including 9,578 patients with moderate and severe TBI enrolled in 10 RCTs and three observational studies showed that the outcome following TBI differs substantially between different examination centers, particularly in Europe (39). Overall, these studies suggest that the IMPACT models, based on a large sample size, can predict mortality and unfavorable outcome at 6 months after injury, reasonably well in patients not undergoing ICP-targeted therapy, and that regional differences should be considered while deciding their clinical application in TBI prognosis.

5. IMAGING STRATEGIES FOR OUTCOME PREDICTION IN SEVERE TBI PATIENTS

Predictive models consider multiple factors, which may be accurate but may not be simple and convenient in clinical application, especially in emergency cases where the therapeutic strategy needs to be decided quickly. It is known that lesions in the brainstem influence patient outcome after severe TBI (40). Hence, imaging techniques, especially magnetic resonance imaging, may be a quick and practical way to predict outcome following injury. Other studies showed that fractional anisotropy and MRI/magnetic resonance spectroscopy-based detection of N-acetyl aspartate/creatine localized in the thalamus, lenticular nucleus, insular cortex, occipital periventricular white matter and pons, have the potential to be used as quantitative outcome-prediction tools during the sub-acute phase of severe TBI (41). MRI has been shown to predict bad outcomes and the time before recovery of consciousness, in diffuse axonal injury patients (42). The amplitude and latency levels of N100, N200 and P300 components of acoustic evoked potentials together with data obtained from diffusion-tensor MRI, have the potential to reliably predict mental recovery in severe TBI (43).
In addition to MRI, early head computed tomography (CT) scans have also been investigated as potential outcome predictors. It was found that CT scans cannot provide sufficient variables to predict disability in surviving patients, although CT characteristics could be correlated with the 6-month outcome in these patients (44). Thus, both MRI and CT techniques have predictive values in determining outcome in severe TBI, while MRI can also predict consciousness recovery and mental recovery.

6. BIOMARKERS FOR OUTCOME PREDICTION IN SEVERE TBI PATIENTS

Biomarkers are indicators of biological processes in normal or disease states. Endocrine abnormalities and inflammatory cytokines have been investigated as biomarkers in severe TBI. In patients (GCS >6), endocrine abnormalities resulted in decreased levels of T3, T4 and testosterone and increased levels of insulin (45). Further, in a study involving 117 adults (28 women and 89 men) with severe TBI, increased estradiol in men and increased testosterone in women seven days post-injury was associated with increased mortality and unfavorable global outcome (46). Hence, endocrine abnormalities may provide predictive information in the prognosis of severe TBI. In addition, the levels of the inflammatory cytokine IL-10 within 30 h following TBI was shown to be a useful independent biomarker in the prognosis of severe TBI, including prediction of GCS severity and hospital mortality (47). The endocrine abnormalities and elevation in inflammatory cytokines may be due to the stress resulting from severe TBI.

S100b, a calcium-binding cytosolic protein, is released into blood from astroglial cells in response to brain injury and disruption of the blood brain barrier. It regulates calcium flux and stimulates astrocyte proliferation (48,49). In severe TBI patients, the mean and peak levels of serum S100b within the first 6 days post-injury, may be an acute mortality predictor (50). However, the blood hemoglobin level had no significant influence on mortality (51).

7. CONCLUSIONS

In determining the prognosis of severe TBI, the utility of both single as well as a combination of multiple predictive factors has been investigated. Combining several clinical parameters may provide more information than single predictors, especially in certain statistical models. The IMPACT and CRASH prognosis calculators, which are based on large sample sizes, have predictive value in estimating long-term outcome. However, they have certain limitations in clinical application. On the other hand,
single predictors, such as the disability status, quantitative cerebral blood flow, ICP, CPP, and duration of coma, are simpler and more convenient to apply in emergency situations. Importantly, imaging techniques like MRI can also predict consciousness recovery and mental recovery in severe TBI, while biomarkers associated with stress can predict severity and mortality. All predictors have limitations when applied to clinical situations. Hence, further studies comparing different predictors and statistical models, is needed. Also, the prediction of clinical outcome in severe TBI patients should be individualized.

8. REFERENCES


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Prediction of severe traumatic brain injury


**Abbreviations:** TBI, Traumatic brain injury; MRI, Magnetic Resonance Imaging; RCTs, randomized controlled trials; SEP, somatosensory evoked potential; CPP, cerebral perfusion pressure; ICP, intracranial hypertension; GCS, Glasgow coma scale; IMPACT, Traumatic Brain Injury; CRASH, Corticosteroid Randomisation after Significant Head Injury; CT, computed tomography

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