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Review Article

Development of prognostic models for patients with traumatic brain injury: a systematic review

Jinxi Gao, Zhaocong Zheng

Department of Neurosurgery, Fuzhou General Hospital, Fuzhou 350025, China

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Abstract: Outcome prediction following traumatic brain injury (TBI) is a widely investigated field of research. Several outcome prediction models have been developed for prognosis after TBI. There are two main prognostic models: International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) prognosis calculator and the Corticosteroid Randomization after Significant Head Injury (CRASH) prognosis calculator. The prognosis model has three or four levels: (1) model A included age, motor GCS, and pupil reactivity; (2) model B included predictors from model A with CT characteristics; and (3) model C included predictors from model B with laboratory parameters. In consideration of the fact that interventions after admission, such as ICP management also have prognostic value for outcome predictions and may improve the models' performance, Yuan F et al developed another prediction model (model D) which includes ICP. With the development of molecular biology, a handful of brain injury biomarkers were reported that may improve the predictive power of prognostic models, including neuron-specific enolase (NSE), glial fibrillary acid protein (GFAP), S-100β protein, tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), myelin basic protein (MBP), cleaved tau protein (C-tau), spectrin breakdown products (SBDPs), and ubiquitin C-terminal hydrolase-L1 (UCH-L1), and sex hormones. A total of 40 manuscripts reporting 11 biomarkers were identified in the literature. Many substances have been implicated as potential biomarkers for TBI; however, no single biomarker has shown the necessary sensitivity and specificity for predicting outcome. The limited number of publications in this field underscores the need for further investigation. Through fluid biomarker analysis, the advent of multi-analyte profiling technology has enabled substantial advances in the diagnosis and treatment of a variety of conditions. Application of this technology to create a bio-signature for TBI using multiple biomarkers in combination will hopefully facilitate much-needed advances. We believe that further investigations about brain injury biomarkers may improve the predictive power of the contemporary outcome calculators and prognostic models, and eventually improve the care of patients with TBI.

Keywords: Traumatic brain injury, Glasgow outcome scale, prediction models, biomarker

Introduction

The history of prognostication after head injury is very long. Both ancient Egyptians and Hippocrates have provided written documentation on the subject. The understanding that existed about the likely outcome after traumatic brain injury (TBI) is illustrated in the Hippocratic aphorism, "No head injury is so serious that it should be despaired of nor so trivial that it can be ignored".

Several prediction models have been developed for prognostication in TBI. They all seek to provide an objective assessment of the likely outcome. The quality of the prognostic models varies, and many of them have not been adequately validated [1]. Some of the prediction models have, however, been validated and these seem to be fairly accurate [2-5].

For the prognosis of the outcome for a specific individual, two prediction models have been developed: the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) prognosis calculator and the Corticosteroid Randomization after Significant Head Injury (CRASH) prognosis calculator [6, 7]. The two models are based on large cohorts, and both claim to have considerable statistical validity.

This review is focused on the development of prognostic models for patients with TBI. The

calibration of prognostic models is also discussed.

The importance of prognostic models

Early determination of prognosis after traumatic brain injury is a priority for relatives and physicians involved in the care of these patients. In a recent multicenter cohort study, about 30% of patients admitted after severe traumatic brain injury will die, and 50% will be moderately disabled, so it is important for clinical experts to have the ability to predict the outcome. The ability to predict outcome in TBI has been sought for multiple reasons. In mild TBI, which accounts for more than 80% of cases, outcome prediction is required to identify patients who would most benefit from early intervention and rehabilitation. In severe TBI, outcome predictors are important for determining the extent of care to provide and, in turn, family counseling. Those who are identified early to have a high risk of developing TBI sequelae would be treated more aggressively and efficiently to mitigate long-term damage.

The intention and hope of the information provided by such prognostic models and calculators are that they can provide support in clinical decision making at the individual level, and also that outcome prediction based on such models, if placed in an appropriate context and discussed by clinical experts, may facilitate the correct assessment of a specific individual's prognosis and thus lead to realistic expectations on the part of the patient's family, as well as provide a rational basis for decisions regarding the aggressiveness of treatment. Prognostic models may also be used as a tool to compare outcomes across institutions, healthcare systems and countries, and may be an essential part of the planning of new studies in the field of brain injury [3, 4, 6, 7].

Prognostic models for patients with TBI

In modern times, many authors have reported on various prediction factors related to outcome, and many of these factors were used in prediction models. Among these, factors found to correlate with poorer outcome are: higher age, lower Glasgow Coma Score (GCS), hypotension, hypoxia, and bilateral fixed and dilated pupils. To date, there are three different approaches to outcome prediction following severe TBI (sTBI). The first is based on admission characteristics such as age, the reaction of pupils, GCS score, GCS motor score, body temperature, blood glucose level, and significant non-cranial injuries, in addition to other factors[8]. The second approach is based on the pathological findings seen on the first available CT scan, and is represented by the Marshall CT classification, and the primarily prognostically oriented Rotterdam score. The third utilizes blood and/or cerebrospinal fluid (CSF) levels of biomarkers of brain injury [9].

However, few of these methods are widely used, possibly because many of them were developed using small samples. Two prediction models have been developed using large cohorts: the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) prognosis calculator and the Corticosteroid Randomization after Significant Head Injury (CRASH) prognosis calculator. Both claim to have considerable statistical validity.

The IMPACT database was developed by Andrew I.R. Maas and his colleagues in 2003. They collected and analyzed the data for 9205 patients from eight randomized controlled trials and three epidemiological studies. They then constructed models for prognostication. The calculator is available on the home page of the IMPACT group (http://tbi-impact.org/).

The prognosis model of the IMPACT study group has three levels. The first level is the basic level or the Core level, which is based on basic clinical data, i.e. age, GCS motor score and pupillary reaction. The second level, the Core + CT or the Extended model, is based on the Core level with the addition of physiological data and data from the CT investigation, i.e. the presence of hypoxia and/or hypotension, the CT scan scored according to Marshall, the presence of subarachnoid hemorrhage and the presence of epidural hematoma. The third and last level is the Core + CT + Lab or Laboratory model, which consists of the two previous levels to which some laboratory data are added, namely glucose and hemoglobin levels.

The CRASH prognosis calculator is based on data from over 10,000 patients who were part of a double-blind randomized placebo-controlled trial on the use of corticosteroids after head injury. These data were analyzed and

used to build a prognostic model. The prognosis calculator is available online (http://www.crash2.1sht.ac.uk). This prognostic model underwent internal validation, as well as, external validation against the IMPACT database. It has been reported, however, that the CRASH prognosis calculator seems to overestimate the risk of mortality and unfavourable outcome [5, 7, 8].

Steyerberg et al. showed that the IMPACT model does not fit the CRASH data well [7]. The IMPACT model for the CRASH data has a C statistic from 0.78 to 0.83 and a *p* value less than 0.001, meaning that the model fitted poorly for the CRASH data. This effect is possibly the result of the IMPACT model being developed based on patients from high-income countries, whereas the CRASH data were mainly collected from low- and middle-income countries. Predictions for TBI patients from low- and middle-income countries may be best obtained from models that are specifically developed for these countries [3, 4].

The modification and progress in prognostic models

There may be several reasons why it is difficult for the prognosis calculator to make good predictions. Neither of the existing prognosis models (the CRASH prognosis calculator or the IMPACT prognosis calculator) takes the treatment protocol used into account, even though mortality and outcome differ between different centers using different guidelines. Since there seems to be a difference in outcome depending on treatment protocol used, one might assume that the prognostic tool should take this into consideration.

Then, in consideration of the fact that interventions after admission, such as ICP management [10, 11], also have prognostic value for outcome predictions and may improve the models' performance, Yuan and his colleagues developed another prediction model including intracranial pressure (ICP). As we know that the prognosis model of the IMPACT study group has three levels. Yuan's prediction model can be considered the fourth level. For risk factors related to outcome, they considered age, sex, cause of injury, motor GCS at admission, pupillary reactivity, CT features, the levels of glucose, hemoglobin (Hb), D-dimer, and serum calcium, intracranial pressure (ICP), and cerebral perfusion pressure (CPP) readings.

Although ICP is considered an important factor for prognosis in patients with TBI, few studies included ICP in a predictive model, probably because ICP monitors were not inserted in all patients. In Yuan's study, 1279 patients with TBI were evaluated. Missing ICP readings restricted the analysis to 227 patients. Even so, the analysis showed that ICP is an important factor associated with outcome. They developed a calculator for predicting the probability of mortality at 30 days and the risk of unfavorable outcome at 6 months, which is available at http://www.6thhosp.com/ks/detail.asp?id=14&artid=4849.

Olivercrona et al. [12] have investigated whether the IMPACT and CRASH prognostic models can be used in patients with severe TBI treated with ICP-targeted therapy based on the Lund concept. They found that the IMPACT prognosis calculator seems to overestimate the frequency of unfavorable outcome and mortality in patients with severe TBI treated with ICP-targeted therapy. Similarly, they found that the CRASH prognostic model overestimated the risk of mortality at 14 days and unfavorable outcome at 6 months. They thus do not advocate the use of the calculators for treatment decisions in individual patients. They further concluded that patients with blunt sTBI admitted within 8 hours of trauma should be treated regardless of their clinical status as long as the initial cerebral perfusion pressure is >10 mmHg.

Brain injury biomarkers and the prognostic models

TBI is a major cause of death and disability and any future research that yields a diagnostic biomarker, or combination of biomarkers along with a practical clinical test, will certainly alter the management of TBI dramatically [13]. Ideally a biomarker should be an easily and reliably measurable molecule with serum/CSF levels that closely correlates with a biological or pathologic process and/or a pharmacological intervention. Currently, biomarkers that can be used to predict clinical outcome are considered surrogate biomarkers or surrogate endpoints.

During the last few decades a rapidly growing number of molecules have been tested as

potential biomarkers of TBI. However, so far no single molecule has been proven specific and sensitive enough to be employed as a comprehensive clinical diagnostic tool to predict the extent of neural tissue damage, or to aid in the care and forecasting of outcome. Nevertheless, there are a handful of molecules that are potential candidates for a complex biomarker panel, including neuron-specific enolase (NSE), glial fibrillary acid protein (GFAP), S-100β protein, tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), myelin basic protein (MBP), cleaved tau protein (C-tau), spectrin breakdown products (SBDPs), ubiquitin C-terminal hydrolase-L1 (UCH-L1), and sex hormones [13].

To date, a total of 40 studies reporting 11 biomarkers were identified in the literature [14-22]. All but a few studies reported statistically significant differences in biomarker expression between groups. S100B, GFAP, TNF-α and MBP appear to have some use in determining the severity of TBI with GFAP and MBP proving to be the most specific for brain trauma. However, these observations vary with the degree of injury and age. To complement this, NSE and UCH-L1 have demonstrated a potential for determining long term-outcome at 6 months. As the majority of biomarkers identified in this review were considered independently, the next step is to identify a combination of sensitive and specific biomarkers, which, together, can provide accurate and reliable prognostic data for TBI. This would most likely include GFAP and MBP for the purposes of specificity, S100B and NSE for sensitivity and possibly UCH-L1 as it has shown some potential in assessing the degree of damage in TBI.

As we know, the IMPACT prognosis model has three levels, the third level is the Core + CT + Lab, or laboratory model. In 2012, Czeiter et al. [23] reported that brain injury biomarkers may improve the predictive power of the IMPACT outcome calculator. They were able to increase the predictive power of the core model by adding three biomarker levels (GFAP in CSF, GFAP in serum, and SBDP145 in CSF) to the core variables (age, GCS motor score, and reaction of pupils). Although there are some limitations to their findings, the results suggest the importance of combining outcome prediction models with biomarker analysis.

The limited number of publications in this field underscores the need for further investigation. Through fluid biomarker analysis, the advent of multi-analyte profiling technology has enabled substantial advances in the diagnosis and treatment of a variety of conditions. Application of this technology to study multiple biomarkers in combination to create a bio-signature for TBI will hopefully facilitate much needed advances.

In conclusion, more and more findings suggest that brain injury biomarkers may improve the predictive power of the contemporary outcome calculators and prognostic models. We believe that further investigations about prognostic models can be used to obtain valid predictions of relevant outcomes in patients with TBI, and eventually improve the care of them.

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Disclosure of conflict of interest

None.

Address correspondence to: Jinxi Gao, Department of Neurosurgery, Fuzhou General Hospital, Fuzhou 350025, China. E-mail: 13859090327@163.com

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