Developing New Prognostic Models for Predicting Outcomes in Severe Traumatic Brain Injury

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ABSTRACT

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Globally, the annual incidence rate of traumatic brain injury (TBI) in all ages is 349 per 100,000 person-years. The incidence of TBI varies across regions, populations, regulations, and health systems; but in general, the rate is expected to be higher in low and middle-income countries (LMICs). As LMICs usually have poor pre-hospital care, delays in patient transfer, lack of facilities and well-trained staff; these make the burden of TBI more devastating and a pressing public health issue. In this dissertation, we focused on several approaches to determine the value of prognostic research in adult patients with severe TBI, test model feasibility and develop new prediction models for TBI population in LMICs, specifically in terms of predicting mortality and functional outcome.

In our narrative review, a search was conducted using PubMed database using the terms “prognostic model” combined with “traumatic brain injury.” The search was limited to articles that included human subjects that were published during 2006 - 2019. We found 20 studies that met the stated search criteria. The results of our review also point out that the majority of current models (85%) were developed from participants in high-income countries (HICs). Additionally, through use of the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist as a tool to assess the quality of reporting prognostic research. We found published articles fell short of describing the flow of patients through the study, explaining the type of biological materials used and their handling methods as well as presenting

estimated effects of key variables with confidence intervals. These findings reveal the gaps in knowledge and also provide recommendations to refine future TBI prognostic research.

We, then, examined the applicability and external validity of the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) and Corticosteroid Randomization after Significant Head Injury (CRASH) models for outcome prediction following TBI using a South-American cohort. A total of 550 patients with severe TBI were enrolled in the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) study and a simultaneously conducted observational study. Although we found the overall performance of all IMPACT and CRASH models was adequate when applied in this dataset, the IMPACT lab model is preferable as it presents a higher discriminative capacity than the CRASH models. Our findings showed the discriminative performance is still reasonable in the dataset of the contemporary clinical studies indicate the IMPACT and CRASH models continuing relevance.

Next, we develop a new prognostic model for severe TBI based on patient admission characteristics and compare this model to the performance of the set of variables in the IMPACT and CRASH core models. We found patient pre-injury comorbidity, anisocoria, glucose level, and motor response post-resuscitation were independent predictors of in-hospital mortality. For functional outcome measured by GOS, respiratory rate at hospital admission, hematocrit, and Glasgow Coma Scale (GCS) score post-resuscitation were independent predictors. Overall, the Thai model for predicting in-hospital mortality had the best performance. The Thailand study reveals the prognostic value of readily available, commonly collected variables like patient vital signs, hematocrit, and glucose level. However, since the data used in the present analysis came from a single site, future external validation should be conducted to confirm model generalizability before applying them more broadly in patients with severe TBI in LMICs.

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CHAPTER 1: Introduction

Traumatic brain injury (TBI) is a global problem that can lead to death and long-term disability.[1] The global annual incidence rate of TBI in all ages is 349 per 100,000 person-years.[2] The highest incidence was reported in Asia, followed by North America, Europe, and Australia.[2] Globally, the World Health Organization predicts that TBI will become one of the leading causes of disability and death by the year 2020.[3] Studies from the Centers for Disease Control and Prevention shows that TBI accounts for one-third of all injuries related to deaths in the US; however, this may underestimate the incidence due to the underdiagnosis of TBI across the spectrum of injuries.[4] TBI has an enormous social and economic impact on patients, their families, the community, and health care systems.[1] Significant efforts have been made over the past few decades to mitigate the morbidity and mortality resulting from TBI; however, its effects are still profound.[4]

The Brain Trauma Foundation published clinical guidelines which have been integrated into TBI care for decades; and the recommendations, especially advanced brain monitoring, have been practiced in many high-income countries (HICs).[5] However, the burden of the disease and the need for care is often greater at hospitals in emerging economies where access to such monitoring may be limited. The proportion of TBIs resulting from road traffic collisions in low and middle-income countries (LMICs) was two times higher than in HICs (56% compares to 25%), especially, in Western Pacific regions and Southeast Asia.[6] A higher burden of TBI, poor pre-hospital care, delays in patient transfer, lack of facilities and well-trained staff highlight the importance of developing evidence-based TBI treatment protocols which can be implemented in low or middle-income countries.[7]

Prognostic models may play a role in assisting with resource utilization decisions as they combine characteristics related to the patient, disease and treatment to predict the possibility of an outcome of interest.[8] The utility of prognostic TBI modelsmay benefit patient, family and physician decision-making.[9] [10] Additionally, validated prognostic models can be more accurate than nurses' predictive capability.[11] Improved prognostic ability can have a particularly important role in LMICs given lack of specialty training in trauma among the healthcare workforce and diagnostic capabilities are limited.[9] The understanding and application of prognostic models can be utilized in these LIMC settings to risk-stratify patients, and may assist nurses and family members with decisions to transfer patients to higher levels of care.

There is a lack of reliable and extensive data on TBI in LMICs.[5] Even though most of the trauma occurs in LMICs, few prognostic models have been developed using these populations.[7 12 13] There is an urgent need for research to develop and validateTBI prognostic models in the LMIC setting, which can inform care teams. The objective of this dissertation is to identify and develop a prognostic model to predict the outcomes among patients with TBI in Thailand, a middle income country with a commitment to improve care for TBI patients.

The Application of Prognostic Models

Information about prognosis and predictive statements can be useful in numerous ways. Estimates of prognosis are an essential element in clinical decision making. The quantification of prognostic risk helps clinicians by influencing decisions regarding the management in individual patients as well as resource allocation, especially when caring for patients with severe acute brain injury in settings where resources may be more limited. Clinicians are likely to allocate intensive care or prioritize treatment to patients with a calculated high likelihood of poor outcome than those with a greater prospect of recovery.[9 14] Estimated prognosis helps prepare patients and their families to be more informed about the goals of care and treatment options. It also facilitates realistic counseling to avoid over-pessimism or create false hopes.[10]

Using baseline prognostic risk to characterize TBI patient populations may facilitate comparisons between different studies. Risk models can also be used as a benchmark for evaluating the quality of care. Moreover, prognostic analysis and identification of covariates are important for stratification and covariate adjustment in clinical trials.[15] In other words, information about prognosis helps determine the appropriate target population and decide if a given intervention has produced an outcome different from that which would have been expected.

Prognostic Models for Traumatic Brain Injury

Prognostic research is the study of relationships between a health outcome at the endpoint and a baseline condition before an individual receives treatment.[16] The primary goal of this area of research is to develop statistical models that combine two or more components of patient data to predict clinical outcome.[12] Early prognostic research for TBI began in 1974 when the Glasgow Coma Scale (GCS) was introduced as an early injury severity assessment tool.[17] The GCS was followed by a standardized approach to evaluate clinical outcomes after brain injury based on the Glasgow Outcome Scale (GOS).[18] These models created the cornerstone for explorations on how to best address the heterogeneity inherent to the TBI population, and are widely used in clinical practice as well as research studies to date.[19 20]

A 2006 systematic review identified 102 prognostic models for TBI reported in 53 studies.[12] Although prognostic studies for TBI are frequently published, there are shortcomings in most of these studies. Most models were developed from a single setting study, and 89% did not conduct external validation, leading to concerns over generalizability. Without external valdation, predictive performance is typically lower in new patient populations.[21] Lack of validation may lead to overfitting, the inclusion of variables which are not contribute to explanatory power. Overfitting can be assessed by internal validation techniques including cross-validation, bootstrapping, and should also be evaluated with external validation.[22] Since most published models were developed from small samples of patients and were rarely validated on external populations, this systematic review identified the needs for better methodological quality in the development of prognostic models for TBI outcomes.

Following that review, two prediction models were developed using large cohorts and externally validated: the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) models[8] and the Corticosteroid Randomization after Significant Head Injury (CRASH) models.[23] The IMPACT database combined patient data from eight randomized controlled clinical trials (RCTs) and three observational studies to give a patient population of 8,509. The CRASH trial was an RCT of the effect of early steroid administration on outcomes after TBI. The CRASH trial enrolled 10,008 patients and is the largest clinical trial ever conducted in patients with TBI. Both studies found that the largest amount of prognostic information is contained in a core set of three predictors: age group, GCS or GCS-motor score, and pupillary reactivity at admission. Table 1 summarizes the characteristics of these two models.

The CRASH and IMPACT models were externally validated on the other datasets, and the validation confirmed good performance.[23] However, the same study reported that the IMPACT model does not fit the CRASH dataset well, especially when the external validation set combined patients from both high and low/middle-income countries.[24] The IMPACT model was developed based upon patients from high-income countries, whereas the CRASH data were developed in the setting of low/middle-income countries. The local level of care also varied: hospital facilities offered more intensive support in high-income countries compared with hospitals in participating low/middle-income countries.[25] This dissertation considers whether predictions for TBI patients from low/middle-income countries may improved from models that are specifically developed for these countries.

Table 1. Comparison of IMPACT and CRASH prediction models

	Study population	Start of treatment	Core model	Extended model	Laboratory model	Predicted outcome
IMPACT	GCS 3-15	≤4 – 24 h	Age, motor score, pupil reactivity	Core model plus: hypoxia, hypotension, Marshall CT classification, SAH, and EDH	CT model plus: glucose and hemoglobin at admission	Mortality and unfavorable outcome (GOS 1-3) at 6 months
CRASH	GCS ≤14	≤8 h	Age>40, GCS score, pupil reactivity, major extracranial injury	Core model plus: petechial hemorrhages, obliteration of the third ventricle or basal cisterns, SAH, midline shift, nonevacuated hematoma		Mortality at 14 days or unfavorable outcome (GOS 1-3) at 6 months

IMPACT, International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury; CRASH, Corticosteroid Randomization after Significant Head Injury; GCS, Glasgow Coma Scale; SAH, subarachnoid hemorrhage; EDH, epidural hematoma; GOS, Glasgow Outcome Scale.

Limited value of general intensive care unit (ICU) scoring systems in patients with TBI

There are several scoring systems commonly used in intensive care unit (ICU) settings such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAP II) and Sequential Organ Failure Assessment (SOFA) scores.[26] The primary purposes of these scoring systems are to quantify the impact of disease severity, aid in reliably predicting patient outcomes, and benchmark the quality of delivered health care. They are developed for use in the general ICU environment and are not disease specific. A study from Raj and colleagues evaluate the usefulness of the APACHE II, SAPS II, and SOFA scores compared to simpler models based on age and GCS in predicting long-term outcome of patients with moderate-to-severe TBI treated in the ICU.[27] The authors found the simple prognostic model shows fairly good prognostic performance and that the use of more complex general ICU scoring systems added little value. TBI is a heterogeneous disease in terms of etiology, pathology, severity and expected outcomes.[20] Hence, disease-specific prognostic models developed using designs and analyses methods adequate to manage the heterogeneity inherent to the TBI population are preferable.

Challenges on applying TBI models developed in high-income countries to the TBI population in low/middle-income countries

An estimated 90% of trauma-related deaths occur in developing countries.[28] The burden of severe brain injury requiring neurointensive care is often greater in emerging economies.[2] Settings with limited resources and low level of interest in reducing the burden of TBI are more likely to have poor patient outcomes.[6 29 30] For example, using data from the Traumatic Coma Data Bank (TCDB), overall expected mortality rate for a hospital with experience and advanced methods in the care of patients with severe TBI is around 35%. In Thailand; however, where pre-hospital services are not well organized and facilities for critical care management are limited, the average mortality rises to almost 50%.[29] Therefore, it is crucial to develop a global community of TBI specialists to share their expertise and resources in order to reduce mortality and morbidity.

Figaji and colleagues examined the differences between HICs and LMICs in demographics, outcomes, and the general use of neuro-critical care monitoring from 117 studies. They used the World Development Indicators to classify the 2012 Gross National Income (GNI) per capita figures for each reviewed country. The results of their study elaborated on the varied nature of TBI care between HICs and LMICs, with differences between patient baseline characteristics, availability of monitoring technology and neurointensive care, and cost-effectiveness of care.[28] In general, TBI patients admitted to ICUs in developing countries tend to be younger and are more likely to be male. Patients living in LMICs had different mechanisms of injury. HICs like the US and Canada have a higher percentage of patients with falls, whereas India had a high proportion of railway crashes, Thailand had many motorcycle injuries, and Tanzania had frequent animal attacks. Figaji et al also found that countries with limited resources have a significantly longer admission time to hospital. In Virginia USA, 50% of patients spent less than 1 hour from the scene of injury to arrival at the hospital; while only 7% of patients in New Delhi, India received hospital care within 1 hour of injury. These differences in baseline characteristics make a difference in selection for ICU admission and may be the reason for divergent results in interventional studies in the TBI population across countries/settings. In addition, many LMICs are underserved areas for neurosurgical care. Ramesh and colleagues reviewed the number of neurosurgeons per population between HICs and LMICs [30]. They found that there is one neurosurgeon for every 65,580 individuals in the US, while the ratio in Rwanda is about one surgeon per 5.7 million people.

Overall, an increase in TBI research can provide more insights and knowledge regarding clinical practice improvements among low/middle-income countries, especially for low-cost interventions. A higher burden of TBI, poor pre-hospital care, delays in patient transfer, lack of facilities and well-trained staff present challenges for research translation of prognostic models in resource-constrained environments. This observation is in line with the previous statement that further development and validation of TBI-specific prediction models in these countries are needed given the global burden of the disease.

Dissertation Elements

A prediction model to estimate clinical outcomes based upon admission criteria is a valuable tool in clinical practice. Early prognosis based on initial findings can influence clinical decisions, and the successful clinical management during the critically acute period can make significant improvements in patient outcomes. Nurses and other providers are on the front line of care and TBI patients can benefit greatly if clinical decision-making is evidence-based. These efforts can contribute to the advancement of clinical studies that are conducted to influence and improve clinical practice. This cooperation is essential to shape future TBI care.

This dissertation aims to review current knowledge about traditional and newly recognized prognostic models for patients with TBI and discuss their value as an important instrument in clinical practice and research. Additionally, this dissertation examines the applicability and external validity of the IMPACT core model in a South-American cohort of patients enrolled in a multicenter randomized controlled trial (BEST TRIP). Finally, a new prognostic model developed from a dataset of patients with severe TBI from a level I trauma center in Thailand is introduced and its prognostic performance is tested by comparing it to IMPACT and CRASH models. Each chapter is formatted in the style of a prospective journal araticle. A brief overview of each chapter is as follows:

Chapter 2. State of the Science of Prognostic Models for Acute Traumatic Brain Injury: A Narrative Review

Chapter 2 presents an overview of prognostic research and its importance for TBI, both research and clinical practice are provided. A discussion of the state of knowledge in current models, their strengths, weaknesses as well as feasibility is made. The standard prognostic model and the recommendations for improving TBI prognosis in LMICs are proposed in this chapter.

Chapter 3. IMPACT and CRASH model for Traumatic Brain Injury: External Validation of the Prognostic Model in a South-American Cohort

External validation evaluates the ability of a prognostic model to reliably predict outcomes in populations apart from the original dataset; few models have been explicitly tested in the context of low and middle income countries, where conditions on the ground vary considerably from those in high income trauma systems and ICUs. In an attempt to predict and improve outcomes of TBI, multiple clinical trials have been conducted. The trial results emphasized the needs for model development sinceit comprised patients from low-income countries where the local level of care might vary. In Chapter 3 we test the external validation of the IMPACT and CRASH prognostic models for examining TBI outcomes in a South-American cohort. The dataset derived from a multicenter randomized, controlled trial (BEST TRIP) was used in the analysis.

Chapter 4. Validation of a Prognostic Model for Outcome after Severe Brain Injury Based on Patient Admission Characteristics in a Thai Cohort

TBI is a leading cause of mortality, morbidity, disability and socioeconomic losses in Thailand as well as other developing countries. Accurate prognostication can help with decisions to transfer to neurosurgical specialist services, the decision to provide aggressive of neurocritical care, and guide the early management of an individual patient. While most of the trauma occurs inLMICs, relatively few prognostic models have been developed using this population. This chapter aims to identify the best performing prognostic model to predict outcomes after the development and validation of prognostic models for hospital mortality and functional outcome at 3-months after injury among Thai patients receiving care for severe TBI.

Chapter 5. Conclusion

Chapter 5 discusses the main findings of this research and its relevance it for the clinical practice of TBI care. It also describes the study limitations and remaining gaps for future research. Lastly, this chapter describes the research and clinical implications for nursing.

CHAPTER 2: State of the Science of Prognostic Models for Acute Traumatic Brain Injury: A Narrative Review

Title: State of the Science of Prognostic Models for Acute Traumatic Brain Injury: A Narrative Review

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Abstract

Objective: It is useful for nurses to apply a standardized prognostic model into their practice in order to provide proper planning and provision of care to TBI patients and their families. This narrative review describes the state of knowledge in current prognostic models in TBI, identifies if there is a current gold standard prognostic model, and provides recommendations for necessary improvements to move toward a clearer direction for prognosis research in TBI.

Data sources: A search was conducted using PubMed database using the terms “prognostic model” combined with “traumatic brain injury.” The search was limited to articles that included human subjects that were published during 2006 - 2019.

Study selection: A total of 47 studies were identified and reviewed. Twenty articles met the following inclusion criteria: had at least 10 or more patients in the study who have GOS unfavorable outcome or death, outcome measure using mortality or Glasgow Outcome Scale (GOS) or GOS Extended, and measured GCS score as a baseline during acute period. Exclusion criteria consisted of pediatric patients, mild TBI, and unable to access the full article

Data synthesis: The REMARK checklist was used to assess the quality of reporting prognostic research. Most studies in this review were retrospective cohort studies and aimed to develop prognostic models for patients with moderate to severe TBI; however, only 33% of new models were validated. Age was the most common predictor, followed by GCS, CT scan with Marshall’s score, pupillary reactivity, glucose level, hypoxia, and anemia. These prognostic variables were measured between 6 – 24 hours after injury. The majority of models (85%) included samples from high-income countries and 25% included patients with the GCS at admission ranging from 3–15. GOS at one month or hospital mortality and GOS at 6 months were the main prognostic outcomes.

Conclusion: This paper has presented the state of knowledge in current models as well as discussed their potential in future research and clinical practice. Although TBI prognosis research has evolved significantly, an analysis based on REMARK checklist has revealed several concerns with their clinical and methodological validity. As such, the paper has provided recommendations to refine future TBI prognosis research. It is important for both clinicians and researchers to understand the inherent limitations of TBI prediction models before integrating them into clinical decision making.

Introduction

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality worldwide.[1] Over half of hospital admissions of persons with severe trauma have associated head injury.[31] The global annual incidence rate of TBI in all ages is 349 per 100,000 person-years.[2] Many campaigns to raise the awareness of preventing such injuries, including helmet and seat belt use, have been undertaken.[32] However when an injury does occur, health care professionals still have limited capacity to alter the severity of this event due to the lack of a drug or therapeutic intervention with proven efficacy to reverse the primary injury.[33] Thus, patient care is geared toward initiating therapeutic strategies to prevent and minimize factors that could extend the initial brain damage, called secondary brain injury, as soon as possible.[34] To provide optimal management, clinicians have to consider the risks and benefits of intervention within the context of prognosis of the individual patient. Accurate and reliable prognostic models for TBI are helpful to inform clinical decision making, resource allocation, and risk stratification as well as statistical analyses of randomized controlled trials (RCTs).

Nurses have a multifaceted role in the care of patients with TBI. As an essential member of the interdisciplinary team, they hold numerous responsibilities to assist with the patient's treatment and recovery. These roles include assessing the patient, coordinating and communicating care, conducting technical and physical care, integrating prescribed therapies, providing emotional support to the patient and their family, advocating for the patient, involving the patient and family in care, and educating the patient and family.[35] One of the most critical responsibilities for nurses in caring for patients with TBI is modifying their plan of care regarding the changes in patient's condition. Usually, such modification relies on the ability to make a clinical decision based on patient characteristics, for example, the Glasgow Coma Scale (GCS) score, age of the patient, the presence of extra-cranial injuries and other comorbidities.[9]

Having a more accurate understanding regarding the prognosis of a patient can help nurses in proper planning and provision of care to these patients as well as their families. On the contrary, incorrect estimation of prognosis can lead to mistakes, where patients who are thought to have a poor prognosis may not be provided optimal care, resulting in a poor outcome.[9 35 36] Also, concern about the outcome is often foremost in the mind of the relative of patients with TBI.[36] In acute care settings, nurses may find it challenging to respond accurately when the families or caregivers of the patients ask about their expectations of recovery. Once the questions are raised, realistic counseling is preferable to over pessimism or the raising of false hopes; and nurses should be well informed concerning what information regarding prognosis should be shared with the families.

Prognosis research is the study of relationships between a health outcome at the endpoint and a baseline condition before an individual receives treatment.[16] The primary goal of this area of research is to develop prognostic models, statistical models that combine two or more components of patient data to predict clinical outcome.[12] Prognostic models can be a more reliable tool than what clinicians can foretell. Without prognostic models, clinicians must rely solely on their own judgment regarding a patient's likely outcome. Individual decision-making may be influenced by a variety of factors including organizational structure, access to supportive resources and education. These factors may potentially adversely affect the patients clinicians treat.[37] There is evidence that a clinician's perception of prognosis can influence the important decision about patient care.[38] [39] For example, a study found that 3.4% of 166 critically ill patients who had ventilation withdrawn on the grounds of end-stage conditions actually survived until discharge from the hospital.[40] The less clinicians perceive about patient's likelihood to survive; the increased the chance of withdrawal of treatment.[39]

Prognostic models have many uses for both research and clinical practice. In the design and analysis of intervention studies, if prognostic factor values are not balanced across treatment groups of interest; they may mask the true effect of an intervention on disease outcome or become potential confounding factors. It is necessary for cohort studies or trials to balance participant characteristics by using prognostic factor values for stratification during the sampling process or as an adjustment in the statistical analysis.[41] Prognostic models can also act as a tool to help clinicians select appropriate tests and therapies in individual patient management since the models are attained from risk assessment to determine the susceptibility of a patient to a particular condition.[38] By identifying patients at high risk for certain complications and implementing interventions to prevent them from happening, this should improve patient outcomes. On the other hand, if prognostic factor values show potential for adverse outcome, clinicians should take information from the models to support decisions on withholding or withdrawing therapy. However, until a causal inference is demonstrated via well-designed RCTs to examine the benefit of intervening on a prognostic factor; we should never assume that applying a particular prognostic model into practice will always improve outcome.[41]

Prognostic factors can be classified into two main levels: individual and population level.[38 41] Individual-level factors consist of biomarkers, imaging, clinical and physiological variables, pathological, or symptoms and behavioral characteristics. Population-level factors in which the exposure of individuals is inferred including area-level social deprivation, health care access and quality, and physical environment (e.g. time interval between trauma onset to the nearest level I trauma center that has in-house neurosurgeons and neurosurgery intensive care unit). Most of the current prognostic model for TBI have included factors from the individual-level, such as Glasgow coma scale (GCS), age, pupil reactivity, and Computed Tomography (CT) scan.[12] It should be taken into account that to the date of this review (January 2019), no TBI study has adopted the population-level factors into a prognostic model. Part of the reason may be due to the difficulties of transferring knowledge from population-level factors into large-scale clinical epidemiological studies. Recently, the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system was designed to establish data sharing across the entire TBI research field. The system contains data, methodologies, and associated tools that facilitate researchers to re-analyze or compare with another dataset. Researchers can find a variety of individual-level factors as well as population-level factors including educational level of caregivers, time using in patients transportation from injury scene to the hospital and more (https://fitbir.nih.gov/). This on-going data sharing system may allow future prognostic research to overcome current deficiencies including small sample sizes and limited discriminative ability and calibration when applied a model to independent data. However, FITBIR does not yet have the capability to facilitate examination of population-level factors

To sum up, Multiple prognostic models for TBI have been developed over several decades, but none of them are widely used in clinical practice. Previous reviews of prognostic studies in TBI have only focused on individual predictors or have been restricted to prognostic models of some type of TBI or outcome.[12] Unless we can build a solid ground for TBI prognostic models to be valid, clinically practical, and userfriendly; it would take some times for clinicians and researchers to expand prognosis research into studies at the population level.

Purpose

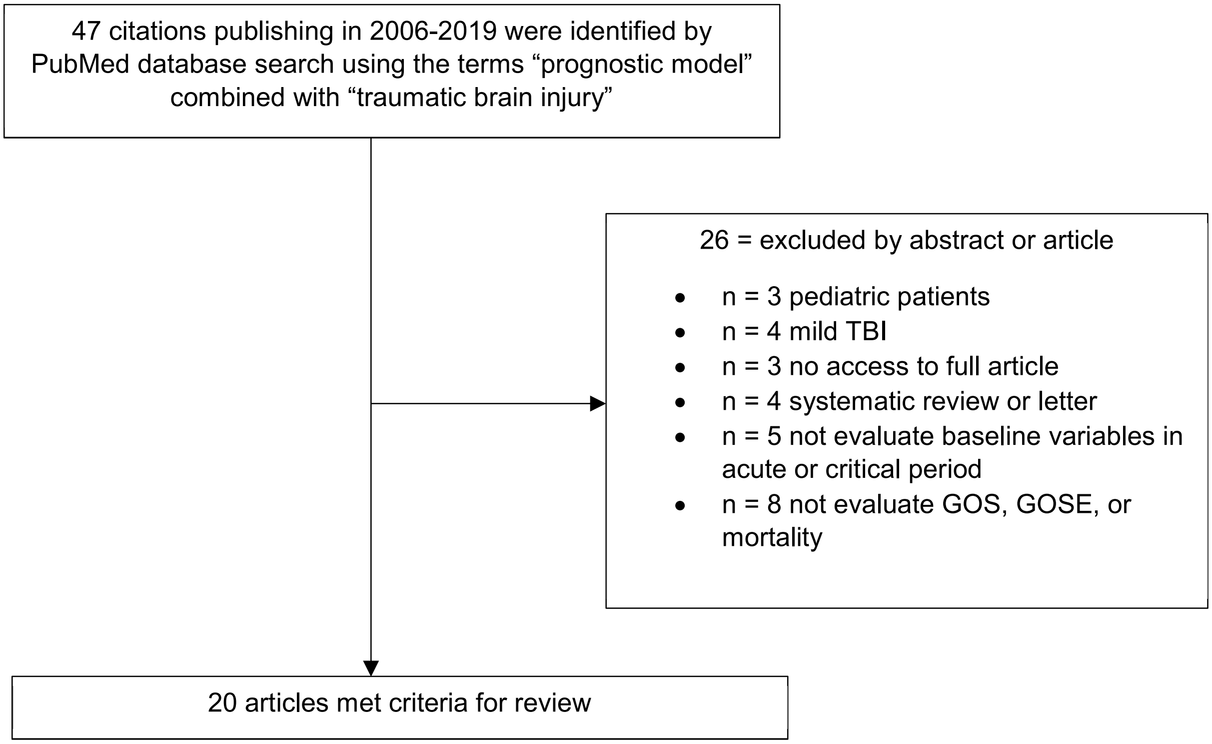
The initial assessment of a patient with TBI is essential in determining the appropriate treatment and acts as a parameter to monitor the evolution of the injury and detect possible complications. However, the heterogeneity of TBI makes an individual patient different from another. It is useful for nurses to apply a standardized prognostic model into their practice in order to provide proper planning and provision of care to these TBI patients as well as their families.

The purpose of this narrative review is to describe the state of knowledge in current prognostic models in TBI, to identify if there is a current gold standard prognostic model, and provide the recommendations for necessary improvements to move toward a clearer direction for prognosis research in TBI.

Methods

The National Library of Medicine's PubMed database was searched in January 2019 using the terms "prognostic model" combined with "traumatic brain injury." The search was limited to articles that included human subjects that were published in the English language during 2006 - 2019. From the initial search, a total of 47 studies were identified and reviewed. Twenty articles met the following inclusion criteria: had at least 10 or more patients in the study who have GOS unfavorable outcome or death, outcome measure using mortality or Glasgow Outcome Scale (GOS) or GOS Extended, and measured GCS score as a baseline during acute period. Exclusion criteria consisted of pediatric patients, mild TBI, and unable to access the full article (see Figure 1). Data extraction was performed, and findings were organized into general themes including types of studies, exposure or prognostic factors, time of measurement, participant characteristics, and outcome measure. Then the quality of reviewed studies was assessed according to criteria for reporting prognostic research by the Reporting Recommendations for Tumor Market Prognostic Studies (REMARK).[42]

Figure 1. Flow chart of search and selection strategy



Results

Type of Studies

Less than half of the articles (40%) were prospective cohort studies (n = 8).[43-50] Five (25%) were designed to validate pre-existing models.[44 46 51-53] Fifteen studies (75%) aimed to develop prognostic models for moderate to severe TBI patients.[7 23 27 45 47-50 54-61] Additionally, five of the 15 new models (33%) were developed and validated using split cohort or cross-validated methods[23 27 48 54 56] (See Table 1).

Type of Exposures or Prognostic Factors

A total of 47 variables were included in the prognostic models. Age was the most common predictor included in the models (90%), followed by GCS (80%), CT scan with Marshall’s score (75%), pupillary reactivity (65%), glucose level (50%), hypoxia (50%), and anemia (40%) (Table 2 the frequency of prognostic factors found in reviewed studies). The variables included in these prognostic models can be grouped into six categories as follow (Table 3): 1) demographic variables were found in 90% of the studies, 2) clinical condition (95%), blood results (55%), brain imaging (75%), treatment (20%), and health care access and quality (10%). It should be noted that information related to treatment and health care access were less included in the analyses compared to other categories.[49 52 59 60]

Time of Measurement

There was a wide range in relation to the timing of measurement for when the prognostic variables were recorded. It could be as soon as within the first six hours post-injury (15%)[48 54 61] or up until the first 24 hours after injury. In this review, seven studies (35%) obtained data upon hospital admission.[1 43-45 47 49 50 53] To date, there is no gold standard of when to measure the prognostic factors, except that clinical and physiologic parameters should be accessed after resuscitation.[15] Since the cardiovascular collapse itself and treatment provided during resuscitation, such as intubation and sedation, could make assessment frequently problematic. Whether scores obtained at earlier assessment moments (pre-hospital or at Emergency Department admission) may be utilized with the same weighting of factors in the reviewed models is uncertain. However according to this review, it may be safe to say that prognostic variables measured between 6 – 24 hours after injury should carry the same weight on clinical outcomes.

Participant Characteristics

A mean of 2,567 patients was included per study (range 56 – 15,190 patients). There were eight studies that included less than 500 patients.[44 45 49 52 53 57 58 61] More than 70% of total participants across all studies were male. Six studies (30%) recruited severe TBI (GCS <8), three studies (15%) developed their model on severe to moderate TBI (GCS <12), and five studies (25%) included patients with the GCS at admission ranging from 3–15. The majority of models (85%) included samples from high-income countries.[23 27 43-46 48 49 53-61] Only three studies (15%) developed or validated their prognostic models in samples from low and middle-income countries.[47 50 52] In one study (5%), the prognostic models were developed in high-income countries and validated in samples from low to middle-income countries.[23]

Outcome Measures

Glasgow outcome scale (GOS) at one month or hospital mortality and GOS at 6 months were the main prognostic outcomes (80%), followed by 12-month GOS (20%). Other outcomes were reported including early death within 48 hours,[48] hospital and ICU lenght of stay,[59] and neurological outcome at 18 months after craniotomy.[58] Even though, evidence suggests that an ordinal approach to analysis of the GOS or GOSE is highly efficient in the analysis phase and can increase statistical power by up to 70%;[15] most of the studies in this review (70%) still dichotomized GOS as favorable (moderate disability or good recovery: GOS 4-5 or GOSE 5-8) vs. unfavorable outcome (death, vegetative state, or severe disability: GOS 1-3 or GOSE 1-4).[23 45 46 49 53 54 56] Collapsing an ordinal measure to a binary scale may discard potentially valuable information. However, the motivation may be because it is intuitively more attractive to clinicians as it allows a simple exploration of a better than expected outcome at the level of individual patients.

Quality of Reviewed Studies

For this article we also assessed the quality of reporting prognostic research by applying the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist items (Table 4).[62] The REMARK checklist provides guidelines for what should be reported in all prognostic factor studies.[41] The criteria were developed based on the rationale that more transparent and complete reporting of studies would enable others to judge the usefulness of the models better and to interpret the study results in the appropriate context.[62] Given the number of prognosis studies reviewed in this paper, it is surprising that the methodology regarding the design and analysis of prognostic factor studies is not more established.[41 63] For example, our analysis using the REMARK checklist found that none of the TBI prognosis studies can draw prognostic effect sizes (such as hazard ratio) and their confidence interval can be extracted for only 58% of the reports (see Table 4).

Out of 22 items in REMARK checklist, the studies from Cicuendez et al. (2018) and Thelin et al. (2017) had the highest numbers of checked items (20/22). While the two studies had slightly different aim (the first study focused on investigating the added prognostic value of Magnetic resonance imaging (MRI) finding in addition to the IMPACT core and extended models,[57] the other aimed to evaluate the new computerized tomography (CT) scoring systems comparing to traditionally systems including Rotterdam CT score and Marshall classification;[60] both studies share the same qualities that other studies in this review lack. The authors specified their imaging techniques and providing the detailed protocols. They also described the flow of patients through the studies and showed the relation of the new developed measures to standard prognostic variables or models. Despite these encouraging qualities, the added value of advanced imaging for prognostic purposes is uncertain, especially with the MRI. Although MRI is sensitive to pathologic changes related to even mild brain injury,[64] 78% of the MRI findings in the study were performed in the first four weeks after injury – indicating it had not been used for early assessing injury severity and prognostication. The reason MRI is not typically indicated for initial evaluation of TBI as it is less sensitive for fractures, takes longer to acquire, and is generally less available. MRI also requires additional safety screening for incompatible medical devices and metalic foreign bodies. As such, it would be challenging for clinicians in acute care settings to apply the information from MRI in their clinical decision making.[64]

The study by Gomez and colleagues has the second highest numbers of checked items (19/22). The model retrieved from this study can be a potential gold standard comparator for future TBI prognosis research.[48] The model consists of variables that are accessible in clinical practice (e.g., GCS, neurological worsening signs, hypoxia, hypotension). As their model did not contain a laboratory-based biomarker as a prognostic factor, it is a less costly tool for clinicians to apply in real-world practice and researchers do not have to worry about sample handling and assay methods and quality control when replicating for future studies. However, in the study report, the authors did not state their pre-specified hypotheses or a rationale for sample size. The specific hypotheses represent assumptions that can be supported or refuted by the results of the study. Whether or not the findings claimed to provide a robust prognostic model depend on how the data are analyzed regarding the hypothesis of the study.[63] Another issue is the explanation of the sample size. In prognostic studies, the most important factor influencing power and sample size is the number of observed events, not the number of patients. If a prognostic model aims to determine an occurrence of a rare complication in severe TBI patients; giving a rationale for the expected effect size will provide a reasonable number of sample size and the level of acceptance chances of false positive findings (type I error).[42] According to the rule of 10 events per variable (EPV) from Peduzzi and Concato (1995),[63] Gomez et al. had overcame these with the appropriate sample size (seven prognostic variables with 192 patients having events).

The studies from Yuan et al. (2012),[54] Raj et al. (2014),[56] Lesko et al. (2014),[45] and Raj et al. (2014)[27] also achieve high scores according to the REMARK checklist (17 – 18). However, researchers or clinicians should be cautious when considering using the models retrieved from these studies as a gold standard comparator for TBI prognostic model. This is because these models did not show the relation of their prognostic factors to standard prognostic variables[45 54] and some failed to describe the type of biological materials used and how to control for their quality.[27 56] The lack of specificity of these issues will make replication and confirmation for future study even harder.

The International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) models developed by Steyerberg and colleagues[23] passes many criteria on the REMARK checklist (16/22). The models were developed in 8,509 patients with moderate to severe TBI from 11 previous studies. External validation was performed on 6,681 patients from the recent Medical Research Council Corticosteroid Randomisation after Significant Head Injury (MRC CRASH) trial. Three final prognostic models were defined, and their ability to predict outcomes were deemed satisfactory (see Table 1 for details). However, some several limitations should be taken into account. First, many factors in the IMPACT model were not recorded in the CRASH data set (e.g., hypoxia, hypotension, extradural hematoma (EDH), glucose, and hemoglobin). Thus, the external validation was only on the core model and some of the extended model; where only the Marshall CT classification and the presence of traumatic subarachnoid hemorrhage (SAH) were added.[44] Also, The data set using for IMPACT and CRASH model development were extracted from multi-center clinical trials conducting between 1985 and 2004.[8] The advancement in TBI care has improved overtime. For the past decades, treatments that are promptly implemented, such as intracranial pressure (ICP) monitoring, multimodal monitoring, and surgical intervention, have been associated with better outcome and lower mortality.[65] The local level of care may also vary between regions, which may result in differences in outcome. Moreover, one of the study in our review found that IMPACT model overestimated risk of mortality and unfavorable outcomes when applying the model in elderly patients with TBI.[53]

The aim of a prognostic model is to provide valid outcome predictions for new patients. To this purpose it is essential to assess both internal and external validities. Internal validation procedures indicate reproducibility in patients similar to the development series, and external validity assesses performance in new patients (could be more recent patients or patients from a different setting.[66] Although there are several limitations of the IMPACT and CRASH models, they are still one of the most established prognostic models in TBI studies.[44 46 52 53 56 58 67] Unless more research has examined the performance of Gomez and colleagues' model in various settings and broader patient characteristics; it is too early to conclude that their model is superior than the IMPACT and CRASH models, regardless the results from REMARK checklist.

Recommendations for Future Research

The Prognosis research strategy (PROGRESS) recently published a framework for developing prognosis research and translating these findings into health-related research [16 41]. The recommendations for future research can be concluded as follow:

a) Study objectives should be presented in the context of existing TBI practice guidelines for planning and implementing prognostic factors into patient management.

b) Studies that aim to develop a new prognostic model for TBI should establish appropriate cohorts with similar health related condition (e.g., diagnosis and symptoms). The ideal classification scheme should be as simple as possible but complex and sensitive enough to fully discriminate TBI into all subtypes of robust therapeutic and prognostic significance. A TBI consensus conference in 2007 suggested classifying TBI according to pathoanatomic schemas (e.g., skull fracture, EDH, SDH, SAH, DAI) as they are most likely to group TBI into categories sharing a common, dominant molecular mechanism of secondary injury and therefore, providing a rational basis for targeted therapies.[20] These cohorts also contribute in validation process and strengthen the validity of study model as well.

c) Statistical analysis methods can be improved by analyzing factors that are continuous variables on continuous scales rather than using unclear cut-points to categorize them. For example, GOS should be exploited as an ordinal scale to relate the outcome to the prognostic risk for individual patients. It is also important to consider fitting an equation in the form that comes as close as possible to a given set of data and avoids predicting a nonlinear situation with a linear model. For instance, age should be analyzed as a continuous variable since there was a curvilinear correlation between age and mortality.

d) For accurate outcome prediction, multiple risk factors need to be considered jointly in a prognostic model because single factors have insufficient predictive value to distinguish patients who will do well from those who will do poorly.[66]

e) Prognostic research studies should improve their transparency of reporting in order to promote the distinction between high-quality research from a low-quality one by adopting standard guidelines in their report such as the REMARK checklist.

f) Researchers should use standard terms for their study variables to enable different readers (clinicians, practitioners from other disciplines, and patients) to interpret research finding appropriately and consistently.

Conclusion

Overall, it may be said that TBI prognosis research has been evolving significantly. Perel and colleagues published a systematic review of prognostic models in TBI in 2006;[12] 65% of models were developed for the first time; our analysis, however, shows an increase of 10% of derivation models (75%). The mean numbers of patients per study included in this review are also higher (2,567 patients compared to 319). The studies have also extended their recruitment to populations in low and middle-income countries (25% in relation to 7% in Perel and colleagues' review). Additionally, our analysis shows similar numbers of models that were validated using split cohort or cross-validated methods compared to the 2006 report (33% versus 38%).

The overall trend in prognosis research has reflected an effort of researchers to improve the quality of TBI prognosis models and transfer this knowledge into practice. For a prognostic model to be useful in real-world practice it should fulfill two requirements: it must not only be methodolgically sound, but also be clinically valid.[63] A methodologically-validated model is one which passes all appropriate statistical checks, including goodness-of-fit on the original data set and unbiased prediction on a new data set. A clinically-validated model is one which performs satisfactorily on a new data set according to context-dependent statistical criteria laid down for it. With an available robust model, clinicians will have a tool to initiate early clinical decision making regarding TBI interventions including the allocation of appropriate resources, and it could provide an efficient means of communicating risk and benefit to patient's family. However, developing prognostic models for TBI is challenging at present because of the very heterogeneous nature of the disease in terms of causes, pathology, severity, and expected outcomes.[20]

This paper has presented the state of knowledge in current models as well as discussed their potential in future research and clinical practice. Although TBI prognosis research has been evolving significantly, an analysis based on REMARK checklist has revealed several concerns in their clinical and methodological validity. As such, the paper has provided recommendations to refine future TBI prognosis research. It is important for both clinicians and researchers to understand the inherent limitations of TBI prediction models before integrating them into daily practice for clinical decision making.

Table 1. Synthesis of findings from reviewed studies

No.	Author (year)	Study/Design/N	Objective	Country of origin	Patients' Characteristics	Study variables/Time at measurement (T)	Model	Outcome	Results
1	Steyerberg et al. (2008)	Predicting Outcome after Traumatic Brain Injury Development and International Validation of Prognostic Scores Based on Admission Characteristics Retrospective cohort study N = 8,509 for model development N = 6,681 for external validation	To develop prognostic models based on admission characteristics with a specific focus on non-Western countries	IMPACT CRASH mostly from low-income countries (75% of participants)	- Moderate and severe TBI (GCS <12) patients aged ≥ 14 y - Data from IMPACT were used to develop model - Data from CRASH were used for external validity	- Demographics (age, sex, race, education) - Indicators of clinical severity (cause of injury, GCS components, pupillary reactivity) - Secondary insults (hypoxia, hypotension, hypothermia) - Blood pressure (systolic, diastolic) - Various CT characteristics - Various biochemical variables T = data were recorded at admission, CT and biochemical within the first 24 h	Three prognostic models were defined: (1) the core model included age, the GCSM, and pupillary reactivity (2) the extended model included the three predictors from the core model plus hypoxia, hypotension, Marshall CT classification, tSAH, and EDH (3) the lab model included the characteristics from the extended model and additional information on glucose and Hb	-The 6 month GOS mortality (GOS=1) versus survival (GOS=2–5) -unfavorable outcome (GOS = 1 or 3) favorable outcome (GOS = 4 or 5)	A prognostic model that combined age, motor score, and pupillary reactivity had an area under the receiver operating characteristic curve (AUC) between 0.66 and 0.84 at crossvalidation. This performance could be improved (AUC increased by approximately 0.05) by considering CT characteristics, secondary insults (hypotension and hypoxia), and laboratory parameters (glucose and hemoglobin).
2	Yuan et al. (2012)	Predicting progressive hemorrhagic injury after traumatic brain injury: derivation and validation of a risk score based on admission characteristics Retrospective cohort study N = 468 for model development N =114 for external validation	To develop and validate a prognostic model that uses information available at admission to determine the likelihood of PHI after TBI.	China	- Adult isolated TBI patients, 73.1% aged < 57 y and 77.8% were male - > 50% injured from motor vehicle accident - GSC 3-8 = 27.4% - GCS 9-12 = 25.4% - GCS 13-15 = 47.2%	- Old age (> 57 years) - low PLT count (< 100*109/L) - prolonged PT (> 14 sec) - high D-dimer level (> 5 mg/L) - high glucose level (> 10 mmol/L) - intra-axial bleeding/brain contusion, and a midline shift > 5 mm) T = data were recorded at admission, CT and biochemical within the first 6 h	- Risk category was calculated by adding the points for each of the following risk factors: age > 57 years (5 points), intra-axial bleeding/ brain contusion (4 points), midline shift > 5 mm (6 points), PLT count < 100*109/L (10 points), PLT count> 100 but < 150*109/L (4 points), PT > 14 sec (7 points), D-dimer > 5 mg/L (12 points), and glucose >10 mmol/L (10 points). - The prognostic index was categorized into 3 groups: low risk (0–13 points), intermediate risk (14–22 points), and high risk (23–54 points).	The 6-month GOS was split into dead (GOS = 1) unfavorable survival (GOS = 2 or 3) favorable survival (GOS = 4 or 5)	- Eight independent prognostic factors were identified and the performance of the risk score was highly reliable when validated in a separate retrospective external validation sample. - The validation cohort, the corresponding PHI rates were 10.9%, 47.3%, and 86.9%. The C-statistic for the point system was 0.864 (p = 0.509 by the Hosmer-Lemeshow test) in the development cohort, and 0.862 (p = 0.589 by the Hosmer-Lemeshow test) in the validation cohort.
3	Ronning et al. (2011)	External validation of a prognostic model for early mortality after traumatic brain injury Prospective cohort study N = 3,136	To externally validate a model for in-hospital mortality in patients with TBI developed by the University of Southern California (USC model) using data from a Norwegian registry	Norway	- TBI patient (GCS <15) with AIS>1 - 71.2% were male and 75.5% aged < 55 - 99% admitted from blunt injury - 67.5% were mild TBI (GCS 13-15), 18.6% were severe TBI	- age > or < 55 y - mechanism of injury: blunt or penetrating - GCS score: 3, 4–8, 9–12, 13–15 - AIS : 1–2, 3, 4, 5 T = data were recorded at admission	- The USC model score Z = -2.740 x (GCS score group) + 1.306 x (head AIS group) + 2.73 x (penetrating injury) + 1.096 x (agegroup) - The variables were assigned values as follows: GCS score 3=1, 4–8=2, 9–12=3, and 13–15=4 AIS 1–2=1, 3=2, 4=3, and 5=4 age, 55 years or younger=0 and older than 55 years=1 penetrating injury status given the value 1 if penetrating and 0 otherwise	- 30-day mortality - in-hospital mortality	- The USC model provided excellent discrimination (AUC =0.93), but had poor calibration (p<0.001) - Subgroup analysis for severe TBI (GCS 4-8) showed a similar result - The USC should not be implemented as a tool for short-term mortality prediction in our TBI population
4	Lesko et al. (2013)	Models of mortality probability in severe traumatic brain injury: results of the modelling by the UK trauma registry Retrospective cohort study N = 802	To develop models to predict survival in a recent cohort of TBI patients within a relatively homogeneous trauma care system	UK	- Pt had to be alive > 3 d to be recorded into the dataset - mean age 38 y (22-58) - 75.2% male - 51.4% severe TBI - 14% had extracranial injury	- age - ISS - extracranial injury: presence or absence - pupillary reactivity: presence or absence - hypoxia (O_2 sat<90%): presence or absence - GCS: mild=13-15, moderate=9-12, severe=<9 - SBP: low=<120, normal=120-150, high=>150 T = data were recorded at admission	- Model A: Age, GCS, Pupillary reactivity, Brain stem injury, Hypoxia, SBP - Model B: Age, GCS, Pupillary reactivity, extracranial injury, Brain stem injury, brain swelling, Hypoxia, SBP	Survival at discharge	- Model A: AUC =0.92, 95%CI, 0.90-0.95 - Model B: AUC = 0.93, 95%CI, 0.91-0.95 - Both models were accurate and reliable

No.	Author (year)	Study/Design/N	Objective	Country of origin	Patients' Characteristics	Study variables/Time at measurement (T)	Model	Outcome	Results
5	Han et al. (2014)	External validation of the CRASH and IMPACT prognostic models in severe traumatic brain injury Prospective cohort study N = 300 for model development	To externally validate two prediction model from CRASH trial and IMPACT model with the national Neuroscience Institute in Singapore	Singapore	- mean age 53 y (35-71) with severe TBI (GCS 3-8) - 47.3% had GCSm ≤4 and 32.4% had major extracranial injury	- age - GCS - pupillary reactivity - major extracranial injury - CT - GCSm - hypoxia - hypotension - Marshall CT classification - Glucose - Hemoglobin T = data were recorded at admission	CRASH had 2 models: 1) age, GCS, pupil reactivity, and the presence of major extracranial injury 2) basic model and the CT model IMPACT had 3 models: 1) age, motor score component from the GCS, and pupillary reactivity = core model 2) core model, hypoxia, hypotension, and Marshall CT classification = extended model 3) extended model, glucose and hemoglobin = laboratory model	CRASH: 14-day mortality and 6 mo GOS: mortality (GOS=1) versus survival (GOS=2–5)	- The CRASH CT model was found to be the most accurate among all the models when used to predict 14 day mortality (AUC=0.83, 95% CI:0.78-0.87) - The IMPACT extended model gave the closet estimate to observe values coinciding with CRASH CT model (AUC=0.81: 95% CI: 0.76-0.86)
6	Lesko et al. (2014)	Comparison of several prognostic tools in traumatic brain injury including S100B Prospective cohort study N = 100 for model development	To identify which tool (a model, a biomarker or a combination of these) has better prognostic strength in traumatic brain injury (TBI).	UK	- pt admitted with head injury (GCS 3-15) with 54% that had GCS <9 - mean age 31 y - 81% were male - 73% had ISS 25-75	- age - GCS - pupillary reactivity - injury cause - S100B T = data were recorded within the first 24 h	Model B: age, GCS, pupillary reactivity and injury cause, S100B Model S100B	3 mo GOS (favorable outcome GOS >4 and survivor GOS > 1)	The 2 model did not differ in their performance - Model B with S100B: AUC=
7	Raj et al. (2014)	Predicting outcome after traumatic brain injury: development of prognostic scores based on the IMPACT and the APACHE II Retrospective cohort study N = 890 (develop cohort = 445, validation cohort = 445)	To create a new set of prediction models for patients with TBI treated in the ICU by combining the IMPACT and the APACHE II	Finland	- median age 58 y (IQR 44-68) - 35% underwent immediate mass lesion evacuation - 34% had GCS 13-15 at admission , 66% GCS 3-12	- age - chronic comorbidity - GCS - GCSm - pupills - hypotension - hypoxia - MAP - RR - HR - BT - PaO2 - FiO2 - pH - Sodium - Potassium - Creatinine - WBC - glucose - hemoblobin - platelet - base excess - INR - Marshall CT T = fisrt CT at admission, the worst physiological and lab values measureed in the first 24 h in ICU	Three new models were created: 1) the IMPACTcore–APAHCE II 2) the IMPACText–APACHE II 3) the IMPACTlab–APACHE II	6 mo mortality unfavorable outcome (GOS 1-3) at 6 mo	IMPACT–APACHE II models was significantly superior, compared to the original IMPACT models (AUC, 0.81–0.82 vs. 0.84–0.85; p < 0.05) for 6-month mortality prediction, but not for unfavorable outcome prediction (AUC, 0.81–0.82 vs. 0.83; p > 0.05).

No.	Author (year)	Study/Design/N	Objective	Country of origin	Patients' Characteristics	Study variables/Time at measurement (T)	Model	Outcome	Results
8	Raj et al. (2014)	Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores Retrospective cohort study N = 1,625 (develop cohort = 844, validation cohort = 781)	To evaluate the usefulness of the APACHE II, SAPS II and SOFA scores compared to simpler models based on age and GCS in predicting long-term outcome of patients with moderate-to-severe TBI treated in the ICU.	Finland	- median age 55 y (IQR 38-66) - all participants had GCS 3-12 with 51% had GCS 3-6	- age - chronic comorbidity - GCS - MAP - RR - HR - SBP - BT - type of ventilator - PaO2 - FiO2 - pH - UOP - BUN - Sodium - Potassium - Bicarbonate - Bilirubin - Creatinine - hematocrit - WBC T =GCS at admission, the worst physiological and lab values measured in the first 24 h in ICU	Based model: GSC + age Tested model: 1) based + APACHE II 2) based + SAP II	6 mo mortality	- The overall six-month mortality was 33%. - The APACHE II +based model AUC 0.79, 95% CI: 0.75, 0.82 - SAPS II+based model AUC 0.80, 95% CI 0.77, 0.83
9	Panczykowski et al. (2012)	Prospective independent validation of IMPACT modeling as a prognostic tool in severe traumatic brain injury Prospective cohort study N = 587	To evaluate the prognostic ability of the IMPACT model to predict 6-month functional outcome and mortality using data from a large, Level I neurotrauma center	US	- age 37.8 (SD 17.4) - all severe TBI, median GCS 6 (IQR 3) - 57% suffered poly trauma (AIS >3)	- Demographics (age, sex) - Indicators of clinical severity (cause of injury, GCS components, pupillary reactivity) - Secondary insults (hypoxia, hypotension, hypothermia) - Blood pressure (systolic, diastolic) - Various CT characteristics - Various biochemical variables T = data were recorded at admission, CT and biochemical within the first 24 h	Three prognostic models were defined: (1) the core model included age, the GCSM, and pupillary reactivity (2) the extended model included the three predictors from the core model plus hypoxia, hypotension, Marshall CT classification, tSAH, and EDH (3) the lab model included the characteristics from the extended model and additional information on glucose and Hb	The 6-month GOS was split into dead (GOS = 1) unfavorable survival (GOS = 2 or 3) favorable survival (GOS = 4 or 5)	- median 6 mo GOS 3 (IQR 3) - 6 mo mortality 41% 1) the core model unfavorable outcome AUC 0.76: mortality AUC 0.78 2) the extended model unfavorable outcome AUC 0.79: mortality AUC 0.783 (3) the lab model unfavorable outcome AUC 0.76: mortality AUC 0.783
10	Munakomi, S. (2016)	A comparative study between Marshall and Rotterdam CT scores in predicting early deaths in patients with traumatic brain injury in a major tertiary care hospital in Nepal Prospective cohort study N = 634	To determine the values of the scoring system and initial CT findings in predicting the death at hospital discharge (early death) in patients with TBI.	Nepal	Not reported	- CT scan **T** = first CT at admission	1) CT Marshall score 2) Rotterdam	6 mo mortality	1) CT Marshall score AUC 0.912 2) Rotterdam AUC 0.929

No.	Author (year)	Study/Design/N	Objective	Country of origin	Patients' Characteristics	Study variables/Time at measurement (T)	Model	Outcome	Results
11	Gomez et al. (2014)	Validation of a prognostic score for early mortality in severe head injury cases Prospective cohort study N = 1,299 (develop cohort =925 validation cohort = 374)	1) To derive a prognostic model for early death (within 48 hours) to be used within the first 6 hours after a severe TBI and to externally validate this model 2) To develop a clinical prediction rule based on the previous model to identify those patients who would be most likely to die early	Spain	- all severe TBI with GCS 3-8 - median age 30 (IQR 21-46) - 77.3% male - 77.4% from traffic accident - 40.6% had shock - 25.8% hypoxia - 57.3% had compressed basal cistern	- age - sex - cause of injury - GCS - GCSm - pupillary reactivity - shock - hypoxia - neurological worsening - tSAH - intraventricular blood - basal cisternal status - EDH - SDH - ICH - midline deviation T =the worse CT and physiological parameter at first 6-h of admission	The fnal model included 7 variables, and it was used to develop a risk score with a range from 0 to 20 points 1) age provided 0, 1, 2, or 3 points depending on the age group (15-35, 36-55, 56-75, 76-95, respectively) 2) motor score provided 0 points, 2 (untestable), or 3 (no response) 3) pupillary reactivity, 0, 2 (1 pupil reacted), or 6 (no pupil reacted) 4) shock, 0 (no) or 2 (yes) 5) SAH , 0 or 1 (severe deposit) 6) cisternal status, 0 or 3 (compressed/absent) 7) EDH, 0 (yes) or 2 (no) 4 risk of early death groups were established: 1) low risk, sum score 0–3 (< 1% predicted mortality) 2) moderate risk, sum score 4–8 (predicted mortality between 1% and 10%) 3) high risk, sum score 9–12 (probability of early death between 10% and 50%) 4) very high risk, sum score 13–20 (early mortality probability > 50%)	early death within 48 h post-TBI	The final model showed a predictive ability of 50% (Nagelkerke R^2), with AUC 0.89 and acceptable calibration (goodness-of-ft test, p = 0.32)
12	Cicuendez et al. (2018)	The added prognostic value of magnetic resonance imaging in traumatic brain injury: The importance of traumatic axonal injury when performing ordinal logistic regression Retrospective cohort study N = 381 (develop cohort =288 validate cohort =93) the develop cohort data were collected during 2000-2014 The validate cohort data were collected during 2014-2016	To investigate the added prognostic value of MRI findings in addition to the IMPACT core and extended models	Spain	- mean age 36.1 (SD 14) - 79% male - 65% traffic accident - 67% GCS < 8 - 78% had MRI done in the first 4 weeks after injury	- age - sex - mechanism of injury - presence of severe extracranial injury - pupillary response - GCS after resuscitation - presence of hypoxia or hypotension - CT imaging T CT = first CT after admission T other variables = within 8 h of admission	The new prognostic model was created: the IMPACT core model (age, the GCSM, and pupillary reactivity) plus MR findings including 1) hemorrhagic subcortical/basal ganglia TAI lesions 2) splenium lesion 3) dorsal brain stem lesion	The 12-month GOSE was categorized as: 1) good: GOSE 7-8 2) moderate: GOSE 5-6 3) severe: GOSE 1-4	Among 178 patients with TAI, lesion in the basal ganglia/thalamus, corpus callosum, and brain stem were associated with poor outcome (p <0.01). The Harrel's c-statistic and AUC of the new model with MR findings were higher than the IMPACT core model alone (AUC 0.72, 95% CI: 0.67-0.77 and 0.68, 95% CI: 0.63-0.73, respectively).
13	Einarsen et al. (2018)	Moderate TBI: Clinical characteristics and a prognostic model of 12-month outcome Prospective cohort study (2004-2013) Total N = 395 (with 160 cases in outcome analysis and 147 in the prediction analysis)	To develop a prognostic model based on admission data, specifically for patients with moderate TBI	Netherlands Norway	- mean age 46 (16-97) - 71% male - 45% traffic accident - 28% alcohol intoxication - mean ISS 17 (9-25)	- preinjury disability - cause of injury - day-of-injury alcohol intoxication - pupillary response - a secondary event at the scene of accident or ED admission: hypoxia, hypotension - transfer from other hospital - intubation - days on ventilator - treatment in a neuro-ICU - LOS in ICU - blood evacuation - ICP monitoring - ISS T = data were recorded at ED admission	Model for predicting GOSE $\leq$ 6: older age, lower GCS score, no day-of-injury alcohol intoxication, presence of SDH, occurrence of a secondary event, preinjury disability	The 12-month GOSE was categorized as: 1) moderate disabled or worse: GOSE $\leq$ 6 2) severely disabled or died: GOSE $\leq$ 4	- 44% were moderately disabled or worse (GOSE $\leq$ 6) and 14% were severely disabled or worse (GOSE $\leq$ 4) - HL test for the model indicated a good model fit (p=0.143) - TheNagelkerke psuedo-R^2 was 0.34. - AUC for the prognostic model was 0.80 (95% CI: 0.75-0.85)

No.	Author (year)	Study/Design/N	Objective	Country of origin	Patients' Characteristics	Study variables/Time at measurement (T)	Model	Outcome	Results
14	Faried et al. (2018)	Feasibility of online TBI prognostic CRASH model as a predictor of mortality of mortality LMIC as Java Retrospective cohort study (July to December 2016) N = 229	To assess the performance of CRASH model for patients with TBI in LMIC	Java	- mean age 32.28 (SD 19.09) - 88% male - 8.3% moderate TBI - 91.7% severe TBI - 93.3% no major extracranial injury	- age - gender - GCS - pupillary reflex - major extracranial injury - time interval T = N/A	The CRASH core model: age, GCS, pupil reaction to light, major extracranial injury	Death at 14 days	- Online CRASH prognostic model reliably predicted 14-day mortality rate (p=0.000) with 91.6% sensitivity and 95% specificity - The AUC for 14-day mortality risk was 0.986 (95% CI: 0.976-0.996)
15	Ho et al. (2018)	Prognostic significance of MRI in patients with severe nonpenetrating TBI requiring decompressive craniotomy Retrospective cohort study N = 56	To compare the ability of IMPACT core model and IMPACT with DAI on MRI	Australia	- age 29 (20-45) - 77% male - GCS 5 (4-8)	- age - gender - GCS - pupillary reflex - CT finding - major extracranial injury - bifrontal craniectomy - ICU LOS - hospital LOS - CRASH risk - IMPACT risk - severity of DAI - number of brain regions with DAI T = N/A	- IMPACT - CRASH - MRI model with the variables including: 1) the presence of DAI on the MRI scan 2) number of brain regions with DAI 3)grading of DAI severity	- neurologic outcome at 18 mo after craniectomy - unfavorable outcome as dependence in average daily activity	- lower GCS, at least one pupil reaction to light, an effaced basal cistern on CT brain scan, and a higher IMPACT and CRASH model predicted risk of unfavorable outcome - The presence of DAI on the MRI scan and number of brain regions with DAI were significantly associated unfavorable outcome, but not be able to predict the outcome as good as IMPACT model (AUC were 0.625 and 0.621 vs. 0.918, respectively; p<0.001 for both comparison
16	Junior et al. (2017)	Prognostic model for patients with TBI and abnormal CT scans Prospective cohort study (2003-2009) N = 1275	To develop prognostic model for assessment of survival chances after TBI based on admission characteristics	Brazil	81% male 75% caucasians 54% road traffic crashes 39% younger than 30 y	- age - gender - cause of injury - ethnic - GCS - anisocoria - CT finding - major extracranial injury T = data were collected upon admission	The new model includes variables: - age - GCS - Marshall scale (2-3 vs. 4-6) - anisocoria (yes/no)	mortality	- Age, presence of anisocoria, Marshall classification and GCS were significantly related to poor outcome - HL test indicated a good model (p=0.24) - AUC was 0.77 (95% CI: 0.74-0.79)
17	Khan et al. (2017)	The impact of Glasgow Coma Scale-age prognosis score on geriatric TBI outcomes Retrospective cohort study (2010-2011) N = 8750	To develop a simple and clinically applicable tool that accurately predicts the prognosis in geriatric TBI patients	National Trauma Data Bank	- age 77.8 (SD 7.1) - GCS 15 (13-15) - head AIS 4 (3-4)	- demographic: age, gender, race, ethnicity - vitals on presentation: heart rate, systolic BP, respiratory rate, temperature, GCS - comorbidities: bleeding disorders, diabetes melitus, hypertension, chronic renal failure	GCS-age prognosis (GAP) score = age/GCS GAP score was classified as: - high: GAP >12 - low: GAP ≤12	- hospital and ICU LOS - ventilator days - in-hospital mortality - discharge disposition	- In-hospital rate mortality was 12.7% and 34.2% of the patients were discharged home. - AUC for mortality was 0.826 (95% CI: 0.812-0.840; p<0.001) - GAP cutoff values of 12 has a specificity of 94% and a sensitivity of 70% - For GCS and age, the AUC for mortality were 0.781 and 0.698, respectively - GAP score has a higher discriminatory power based on the AUC for mortality compared with age or GCS alone.
18	Thelin et al. (2017)	Evaluation of novel computerized tomography scoring system in human TBI: An observational multicenter study Retrospective cohort study (2005-2014) Total N = 1115 (Sweden = 720, Finland = 395)	1) To evaluate the Stockholm and Helsinki CT scores for predicting functional outcome, in comparison with the Rotterdam CT score and Marshall classification 2) To assess what additional prognostic value the CT scoring systems contribute to a clinical prognostic model	Sweden Finland	- age 54 (36-65) - 75% male - 62% fall - 25% had significant extracranial injury - 54% GCS 3-8	- age - GCS at admission - pupil responsiveness - intracranial surgery - hemoglobin - glucose level - CT scan T = data were collected upon hospital admission T for CT = initial head CT scan after trauma	- Marshall CT classification: Grade I, II, III, IV, V+VI - Rotterdam CT score: basal cisterns/midline shift, epidural mass lesion,intraventricular blood or tSAH = total scores range from 1-6 - Helsinki CT score: mas lesion type, mass lesion size, IVH, basal cisterns = total scores range from -3 to 14 - Stockholm CT score: tSAH score, tally	GOS at 12 months was categorized as: - 1, 2, 3, 4, 5 - 1-3 vs. 4-5 - 1 vs. 2-5	- overall 43% of patients had unfavorable outcome (GOS 1-3) - Stockholm CT score was more accurate, follow by the Helsinki CT score, Rotterdam CT score and Marshall CT classification (Nagelkerke's pseudo R^2 range 0.24-0.28, 0.18-0.22, 0.13-0.15, and 0.03-0.05, respectively) - Stockholm CT score added the prognosis value to IMPACT model of 6% and Helsinki's added 4% - Aggregrate tSAH component of the Stockholm CT score was the strongest predictor of unfavorable outcome

No.	Author (year)	Study/Design/N	Objective	Country of origin	Patients' Characteristics	Study variables/Time at measurement (T)	Model	Outcome	Results
19	Wan et al. (2017)	Is it reliable to predict the outcome of elderly patients with severe TBI using the IMPACT prognostic calculator? Retrospective cohort study (2008-2015) N= 137	To investigate the efficacy and usability of the IMPACT prognostic calculator for assessing prognosis in elderly patients with TBI	China	- age 73.1 (65-89) - 70.8% male - 37.2% older than 75 - 53.3% fall - 16.1% received anticoagulants or antiplatelet drugs	- Demographics (age, sex) - Indicators of clinical severity (cause of injury, GCS components, pupillary reactivity) - Secondary insults (hypoxia, hypotension, hypothermia) - Various CT characteristics - Various biochemical variables T = N/A	- IMPACT core model - IMPACT extened model - IMPACT lab model	GOS at 6 months: - death: GOS 1 - unfavorable outcome: GOS ≤3	The AUC for mortality of each model were: - IMPACT core model 0.76 - IMPACT extened model 0.76 - IMPACT lab model 0.73 The AUC for unfavorable outcome of each model were: - IMPACT core model 0.80 - IMPACT extened model 0.79 - IMPACT lab model 0.77 These findings suggest fair discrimination. The actual outcomes in a cohort of elderly patients with severe TBI were slightly better than the expected outcome.
20	Watanabe et al. (2018)	Outcomes after TBI with concomitant severe extraacranial injuries Retrospective cohort study (2007-2015) Total N = 485	To examine the influence of concomittant SEI on the mortality or functional outcome of brain injury	Japan	- Isolated TBI 343 - TBI with SEI 142 - age 51.3 (SD 26.7) - 70.1% male - 55.1% traffic accident - 28% head operation - 45.4% opertation in other areas	- age - vital signs - head injury diagnosis - operation - head AIS - ISS - RTS - LOS - coagulation T = within 6 h after the ED admission	SEI model: age, GCS, LOS, presence of SEI, hypotension, coagulopathy	- hospital mortality: GOS 1 at discharge - unfavorable outcome: GOS ≤3 at hospital discharge	- Mortality was 17.8% in the isolated TBI group, and 21.8% in the TBI with SEI group (p=0.38) - The isolated TBI group has a better functional outcome when compares to the TBI with SEI group

Table 2. Frequency of prognostic factors found in reviewed studies

No.	Author (year)	Age	Sex	Race	Education	Transfer from other hospital	T to admit	Chronic morbidity	Cause of injury	Alcohol intoxication	Extracranial injury	Mechanism of injury	GCS	GCSm	Neuro worsening	Pupil reactivity	Hypoxia	Hypotension	Hypothermia	SBP	DBP	Mean BP	HR	RR	BT	Treatment in a nuero-ICU	Type of ventilator	PaO2	FiO2	pH	O2 Sat	BE	INR	Glucose	Hb	Platelet	PT	UOP	BUN	Sodium	Potassium	Bicarbonate	Bilirubin	Creatinine	WBC	D-dimer	MRI	CT
1	Steyerberg et al. (2008)	●	●	●	●				●				●	●		●	●	●	●	●														●	●													●
2	Yuan et al. (2012)	●																																●		●	●									●		●
3	Ronning et al. (2011)	●									●	●	●																																			
4	Lesko et al. (2013)	●									●		●			●	●			●																												●
5	Han et al. (2014)	●									●		●	●		●	●	●																●	●													●
6	Lesko et al. (2014)								●		●		●			●						●									●			●	●													●
7	Raj et al. (2014)	●						●					●	●		●	●	●				●	●	●	●			●	●	●		●	●	●	●	●				●	●			●	●			●
8	Raj et al. (2014)	●						●					●							●		●	●	●	●		●	●	●	●				●				●	●	●	●	●	●	●	●			
9	Panczykowski et al. (2012)	●	●						●				●			●	●	●	●	●	●													●	●													●
10	Munakomi, S. (2016)	●																																														●
11	Gomez et al. (2014)	●	●						●				●	●	●	●	●	●																														●
12	Cicuendez et al. (2018)	●	●								●	●	●			●	●	●																														●
13	Einarsen et al. (2018)	●	●			●		●	●	●						●	●	●								●	●																					
14	Faried et al. (2018)	●	●				●				●		●			●																																
15	Ho et al. (2018)	●	●								●		●	●		●	●	●																●	●												●	●
16	Junior et al. (2017)	●	●	●					●		●		●			●																																●
17	Khan et al. (2017)	●	●	●				●					●							●			●	●	●	●	●																					
18	Thelin et al. (2017)	·									●	●	●			·										●								●	●													●

No.	Author (year)	Age	Sex	Race	Education	Transfer from other hospital	T to admit	Chronic morbidity	Cause of injury	Alcohol intoxication	Extracranial injury	Mechanism of injury	GCS	GCSm	Neuro worsening	Pupil reactivity	Hypoxia	Hypotension	Hypothermia	SBP	DBP	Mean BP	HR	RR	BT	Treatment in a nuero-ICU	Type of ventilator	PaO2	FiO2	pH	O2 Sat	BE	INR	Glucose	Hb	Platelet	PT	UOP	BUN	Sodium	Potassium	Bicarbonate	Bilirubin	Creatinine	WBC	D-dimer	MRI	CT
19	Wan et al. (2017)	●	●	.	.	.	.		●				●	●		●	●	●	●															●	●													●
20	Watanabe et al. (2018)	●	●									●								●			●	●												●	●									●		●
	Frequency (n)	18	11	3	1	1	1	2	7	1	9	4	16	6	1	13	10	9	3	6	1	3	4	4	3	3	3	2	2	2	1	1	1	10	8	3	2	1	1	2	2	1	1	2	2	2	1	15
	%	90.00	55.00	15.00	5.00	5.00	5.00	10.00	35.00	5.00	45.00	20.00	80.00	30.00	5.00	65.00	50.00	45.00	15.00	30.00	5.00	15.00	20.00	20.00	15.00	15.00	15.00	10.00	10.00	10.00	5.00	5.00	5.00	50.00	40.00	15.00	10.00	5.00	5.00	10.00	10.00	5.00	5.00	10.00	10.00	10.00	5.00	75.00

Table 3. Prognostic factor categories

Categories	Variables
Demographic	age, gender, and ethnicity
Clinical condition	Comorbidity, cause of injury, mechanism of injury, alcohol intoxication, extracranial injury, GCS component, neuro-worsening, pupillary status. Hypoxia, hypotension, hypothermia, vital signs
Blood results	Blood gases analysis, blood chemical, anemia, coagulation, glucose level
Brain imaging	CT, MRI
Treatment	ICP monitoring, ventilatory support, brain surgery
Health care access and quality	Educational level, transferred from another hospital, time duration from the trauma scene to study hospital

GCS, Glasgow Coma Scale; CT, computed tomography; MRI, magnetic resonance imaging; ICP, intracranial pressure

Table 4. Quality assessment for reporting prognostic research based on REMARK checklist items

Study	Introduction			Materials and Methods										Results							Discussion		Total checked items
	State the marker examined	the study objectives	pre-specified hypotheses	- describe Pt. characteristics - Pt. source - Inclusion & Exclusion Criteria	- Describe treatments received - how chosen	- Describe type of biological material used - methods of preservation and storage	- Specify the assay method used and provide a detailed protocol - Specify whether and how assays were performed blinded to the study endpoint	- State the method of case selection - Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time	Precisely define all clinical endpoints examined	List all candidate variables initially examined	Give rationale for sample size	Specify all statistical methods and how missing data were handled	Clarify how marker values were handled in the analyses	Describe the flow of patients through the study	Report distributions of basic demographic characteristics	Show the relation of the marker to standard prognostic variables	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect	For key multivariable analyses, report estimated effects with confidence intervals	Provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance	report results of further investigations	Interpret the results in the context of the pre-specified hypotheses and other relevant studies	Discuss implications for future research and clinical value	
Predicting Outcome after Traumatic Brain Injury Development and International Validation of Prognostic Scores Based on Admission Characteristics		●	●	●	●	●		●	●	●	●	●	●		●	●	●	●	●	●	●	●	16
Predicting progressive hemorrhagic injury after traumatic brain injury: derivation and validation of a risk score based on admission characteristics	●	●	●	●		●		●	●	●		●	●	●	●		●	●	●	●	●	●	18
External validation of a prognostic model for early mortality after traumatic brain injury	●	●	●	●	●			●	●			●	●		●	●	●			●	●	●	14
Models of mortality probability in severe traumatic brain injury: results of the modelling by the UK trauma registry		●		●		●		●	●	●		●	●	●	●		●	●	●	●	●	●	16
External validation of the CRASH and IMPACT prognostic models in severe traumatic brain injury		●		●	●	●		●	●	●		●	●		●	●	●	●	●	●	●	●	17
Comparison of several prognostic tools in traumatic brain injury including S100B	●	●		●	●	●	●	●	●	●		●	●		●		●		●	●	●	●	17
Predicting outcome after traumatic brain injury: development of prognostic scores based on the IMPACT and the APACHE II	●	●	●	●	●			●	●	●		●		●	●	●	●	●	●	●	●	●	18

Study	Introduction			Materials and Methods										Results							Discussion		Total checked items
	State the marker examined	the study objectives	pre-specified hypotheses	- describe Pt. characteristics - Pt. source - Inclusion & Exclusion Criteria	- Describe treatments received - how chosen	- Describe type of biological material used - methods of preservation and storage	- Specify the assay method used and provide a detailed protocol - Specify whether and how assays were performed blinded to the study endpoint	- State the method of case selection - Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time	Precisely define all clinical endpoints examined	List all candidate variables initially examined	Give rationale for sample size	Specify all statistical methods and how missing data were handled	Clarify how marker values were handled in the analyses	Describe the flow of patients through the study	Report distributions of basic demographic characteristics	Show the relation of the marker to standard prognostic variables	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect	For key multivariable analyses, report estimated effects with confidence intervals	Provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance	report results of further investigations	Interpret the results in the context of the pre-specified hypotheses and other relevant studies	Discuss implications for future research and clinical value	
Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores	●	●	●	●	●			●	●			●		●	●	●	●	●	●	●	●	●	17
Prospective independent validation of IMPACT modeling as a prognostic tool in severe traumatic brain injury	●	●		●				●	●	●		●			●		●			●	●	●	12
A comparative study between Marshall and Rotterdam CT scores in predicting early deaths in patients with traumatic brain injury in a major tertiary care hospital in Nepal	●	●	●	●		●			●								●			●	●	●	10
Validation of a prognostic score for early mortality in severe head injury cases	●	●		●	●	●		●	●	●		●	●	●	●	●	●	●	●	●	●	●	19
The added prognostic value of magnetic resonance imaging in traumatic brain injury: The importance of traumatic axonal injury when performing ordinal logistic regression	●	●	●	●	●	●	●	●	●	●		●	●	●		●	●	●	●	●	●	●	20
Moderate TBI: Clinical characteristics and a prognostic model of 12-month outcome	●	●	●	●		●	●	●	●	●		●	●	●	●		●	●		●	●	●	17
Feasibility of online TBI prognostic CRASH model as a predictor of mortality of mortality LMIC as Java	●	●	●	●		●		●	●	●	●	●			●		●			●	●	●	10

Study	Introduction			Materials and Methods										Results							Discussion		Total checked items
	State the marker examined	the study objectives	pre-specified hypotheses	- describe Pt. characteristics - Pt. source - Inclusion & Exclusion Criteria	- Describe treatments received - how chosen	- Describe type of biological material used - methods of preservation and storage	- Specify the assay method used and provide a detailed protocol - Specify whether and how assays were performed blinded to the study endpoint	- State the method of case selection - Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time	Precisely define all clinical endpoints examined	List all candidate variables initially examined	Give rationale for sample size	Specify all statistical methods and how missing data were handled	Clarify how marker values were handled in the analyses	Describe the flow of patients through the study	Report distributions of basic demographic characteristics	Show the relation of the marker to standard prognostic variables	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect	For key multivariable analyses, report estimated effects with confidence intervals	Provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance	report results of further investigations	Interpret the results in the context of the pre-specified hypotheses and other relevant studies	Discuss implications for future research and clinical value	
Prognostic significance of MRI in patients with severe nonpenetrating TBI requiring decompressive craniotomy	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●			●	●	●	●	15
Prognostic model for patients with TBI and abnormal CT scans	●	●		●	●	●			●	●		●			●		●	●	●	●	●	●	15
The impact of Glasgow Coma Scale-age prognosis score on geriatric TBI outcomes	●	●		●		●			●	●		●	●		●	●	●	●	●	●	●	●	16
Evaluation of novel computerized tomography scoring system in human TBI: An observational multicenter study	●	●		●	●	●	●	●	●	●		●	●		●	●	●	●	●	●	●	●	20
Is it reliable to predict the outcome of elderly patients with severe TBI using the IMPACT prognostic calculator?	●	●		●		●			●			●			●					●	●	●	10
Outcomes after TBI with concomitant severe extraacranial injuries	●	●	●	●	●	●	●	●	●	●		●			●					●	●	●	15
Frequency (n)	18	20	6	19	12	16	6	14	20	16	0	18	12	8	18	8	16	12	13	20	20	20	
%	90	100	30	95	60	80	30	70	100	80	0	90	60	40	90	40	80	60	65	100	100	100	

CHAPTER 3: IMPACT and CRASH Models for Traumatic Brain Injury: External Validation of Prognostic Models in a South-American Cohort

Title: IMPACT and CRASH model for Traumatic Brain Injury: External Validation of the Prognostic Model in a South-American Cohort

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Keywords: Brain injury, external validation, prognostic model, outcome, low and middle-income countries

Target journal: Injury Prevention

*Paper formatting is in style of the prospective journal

Abstract

Background: Prognostic models are useful for decision making in clinical practice as they provide guidance and objective information for traumatic brain injury (TBI) patient management, as well as communication with the relatives of patients, and resource allocation. As a means to develop a robust prognostic model, the more diverse the settings in which the system is tested and found to be accurate, the more likely it will be generalizable to untested settings.

Purpose: This study aimed to externally validate the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) and Corticosteroid Randomization after Significant Head Injury (CRASH) models for low and middle-income countries (LMICs) using a dataset of patients with severe TBI from South-American cohort. The secondary aim is to determine which model indicated a better fit in this population.

Setting: Nine hospitals with neurological intensive care units in Argentina, Brazil, Bolivia, Colombia, and Equador.

Participants: Patients older than 12 years of age who suffered severe closed head injury, as defined by a Glasgow Coma Scale (GCS) score of $\leq$8 points on admission (with a score on the GCS motor component of 1-5 if the patient was intubated), or a higher GCS score on admission that dropped to the specified range within the first 48 hours after injury. A total of 550 patients with severe TBI were enrolled in the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) study and a simultaneously conducted observational study.

Design: Prospective data were collected from the South American dataset and external validation study was conducted.

Measures: Patient admission characteristics were extracted to predict unfavorable outcome (Glasgow Outcome Scale:GOS $\leq$3) and mortality (GOS 1) at 14 days or 6 months.

Results: A total of 466 patients with GOS at 6 months were included in the analysis. Of these, 48% had unfavorable outcome at 6 months, including 38% who haddied. The AUC values were 0.683-0.775 and 0.640-0.731 for the IMPACT and CRASH models respectively. The IMPACT CT model had the highest AUC for predicting unfavorable outcomes, and the IMPACT Lab model had the best discrimination for predicting 6-month mortality. The discrimination for both the IMPACT and CRASH models improved with increasing complexity of the models. Calibration revealed that there were disagreement between observed and predicted outcomes in the IMPACT and CRASH models.

Conclusion: The overall performance of all IMPACT and CRASH models was adequate when used to predict outcomes in the dataset from South America cohorts. However, some disagreement in calibration suggests the necessity for updating prognostic models to maintain currency and generalizability.

Keywords: Brain injury, external validation, prognostic model, outcome, low and middle-income countries

BACKGROUND

Traumatic brain injury (TBI) is a leading cause of death and long-term disability around the globe. Despite advancements in prevention and treatment, there have not been significant improvement in TBI outcomes.[1] Globally, the annual incidence rate of TBI in all ages is 349 per 100,000 person-years.[2] The incidence of TBI varies across regions, populations, regulations, and health systems; but in general, the rate is expected to be higher in low and middle-income countries (LMICs).[6] A recent study found that the Latin American and Caribbean region, where approximately 36% of the population are living below the poverty line, has the highest incidence rate of TBI compared to other regions (169 per 100,000 person-years).[68] Since LMICs usually have poor pre-hospital care, delays in patient transfer, lack of facilities and well-trained staff; these make the burden of TBI more devastating and a pressing public health issue.[7]

Prognostic models are useful for decision making in clinical practice as they provide guidance and objective information for TBI patient management, as well as communication with the relatives of patients, and resource allocation.[69] In addition, prognostic models can be used to improve the classification of TBI based on prognostic risks, which allow for development of more precise treatment options as well as better design and analysis of clinical trials.[20] Many prognostic studies for TBI patients have been published over the years. However, a systematic review by Perel et al. in 2006 shows that there are deficiencies in those models regarding their generalizability to other populations - mostly because of the lack of external validation.[12]

When developing prognostic models, external validation is essential to determine the ability of the model to reliably predict outcomes in new populations; different from the development population dataset, particularly, in time and place.[66] Following Perel's review, two prediction models were developed using large cohorts and were externally validated: the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) model[8] and the Corticosteroid Randomization after Significant Head Injury (CRASH) model.[23]

The IMPACT database combined patient data from eight randomized controlled clinical trials (RCTs) and three observational studies to give a patient population of 8,509. The CRASH trial was an RCT of the effect of early steroid administration on outcome after TBI. The CRASH trial enrolled 10,008 patients and is the largest clinical trial ever conducted in patients with TBI. Both studies showed that the largest amount of prognostic information is contained in a core set of three predictors: age, Glasgow coma scale (GCS) or GCS-motor score, and pupillary reactivity at admission.

The CRASH and IMPACT models were initially reciprocally validated externally on other datasets.[23] This validation confirmed good discrimination, but the IMPACT model did not calibrate well when the dataset combined patients from both high and low/middle-income countries together.[24] 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/middle-income countries. This difference may have resulted from variations in the local level of care, or more extensive the hospital facilities in high-income countries compared to the low/middle-income countries that participated in the trial.[25]

As a mean to develop a robust prognostic model, the more diverse the settings in which the system is tested and found accurate, the more likely it will be generalizable to untested settings.[63] Therefore, this study aims to externally validate the IMPACT and CRASH model using a South-American cohort and to determine which model provides a better fit in this population. The analysis is based on the data collected in the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) study,[70] a multicenter randomized controlled trial (RCT) comparing the effectiveness of protocol based on intracranial pressure monitoring vs. imaging and clinical examination in patients with severe TBI. Additionally, patient data from an observational study conducted simultaneously with the BEST-TRIP study were included to increase the available sample size.

MATERIALS AND METHODS

Patients and samples

A retrospective cohort study was conducted using data combined from the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) study and an observational study. The BEST-TRIP study included 324 patients from four hospitals in Bolivia and two hospitals in Ecuador.[70] Data were collected between September 2008 and May 2012. The study hospitals had intensive care units

(ICUs) staffed with intensivists, 24-hour computed tomographic (CT) services, and round-the-clock neurosurgery coverage.[71] The other 226 subjects were enrolled in an observational study from Argentina, Brazil, and Colombia. The observational study was conducted simultaneously with the BEST-TRIP trial using the same enrollment criteria. Patients in the observational study centers were treated with usual care where some hospitals routinely employed ICP monitoring and some did not.

Inclusion criteria

All of the subjects were older than 12 years of age and suffered from severe closed head injury, as defined by a GCS score of $\leq$8 points on the admission (with a score on the GCS motor component of 1-5 if the patient was intubated) or a higher GCS score on admission that dropped to the specified range within the first 48 hours after injury. All patients in the RCT were admitted to the study hospitals within 24 hours of injury. All the participants required ICU level care where they were randomly assigned to the intracranial pressure monitoring (ICP) group or imaging and clinical examination (ICE) group. The ICP group was treated to maintain an intracranial pressure of less than 20 mm Hg, in accordance with the United States Brain Trauma Foundation Guidelines for the management of severe TBI. The care for ICE group was provided by a protocol based on the pretrial standard for care at the participating hospitals (for more information see the description of treatment protocols in Carney et al., 2012).[71]

Exclusion criteria

Patients were excluded if their GCS score was 3 with bilateral fixed and dilated pupils, and those with an injury believed to be unsurvivable. Patients whose family were unable to provide consent, were pregnant or a prisoner, or had a pre-existing neurological disability that would not allow follow-up were also excluded from the study.

End-points

Follow-up was conducted in person, when possible, with the patient using a questionnaire and neuropsychological measures. Primary outcomes of this study were the Extended Glasgow Outcome Scale (GOSE; an eight-point scale ranging from death to complete recovery) and mortality at two weeks and 6 months post-injury. For comparison with the IMPACT and CRASH data and model validation, the GOSE was collapsed into the five-point GOS (for details of the comparison of GOS and GOSE, see the Supplementary Appendix). We then dichotomized the score as unfavorable if the patient GOS was $\leq$3 (i.e., death or vegetative state or severe disability) or favorable if GOS score was >3 (i.e., good recovery or moderate disability). We also classified patients as having died (GOS 1) or survived (GOS 2-5).

Risk factors definition

Age was measured in years. The GCS and motor scores post-resuscitation were recorded. The post-resuscitation pupillary response from each eye was recorded as “no response,” “response,” or “unable to test.” Major extracranial injury (MEI) was determined according to the Abbreviated Injury Scale (AIS) score. A patient was considered to have an MEI if at least one of the extracranial body regions that were evaluated had an AIS score $\geq$3 or $\geq$2 points in two extracranial regions in the same patient. Hypoxia was defined as an oxygen saturation of <90% at the first assessment. Hypotension was defined as a systolic blood pressure of <90 mm Hg. Marshall CT classification categorized injuries as different levels of diffuse lesions based on basal cistern compression and midline shift, or focal lesions, depending on whether lesion volume exceeds 25 cm^3 (see the Supplementary Appendix for details).[72] Subarachnoid hemorrhage (SAH) and epidural hematoma (EDH) were diagnosed following the patient’s first CT imaging.

Handling of missing data

We discussed potential causes of missing data with the researchers who conducted the BEST-TRIP study. They were not aware of any data used in the present study that were not missing at random (MAR). Thus, we used multiple imputations as an approach to handle missing data among the predictors. [73] For cases where specific data on eye opening (31%), verbal response (51%), and motor response (26%) were missing, the total GCS were collected and available for imputation and analysis. All the GCS information from the parent study was used for GCS total or GCS motor response. Patients with missing outcome data were excluded from the analysis.

Statistical analysis

A descriptive analysis was carried out. Quantitative variables were expressed using mean and standard deviation or median and interquartile range (IQR), depending on whether or not they followed a normal distribution. Qualitative variables were represented as frequencies and percentage. Then, we determined the generalizability of the IMPACT models and CRASH models for LMICs when applied to the BEST-TRIP dataset by assessing the following measures: calibration, discrimination, and overall model performance measure using R^2.[66] Regression coefficients and intercepts for both the IMPACT and CRASH models were obtained from their prognostic calculator website (Supplemental Content, Appendix 4).

Calibration refers to the agreement between the observed outcome frequencies and predicted probabilities from the model.[15] If we predict 10% mortality, the actual observed mortality on average should be 10%. The calibration was assessed using Hosmer-Lemeshow goodness-of-fit (H-L) test.[74] This test divides subjects into deciles based on predicted probabilities, and then compares a χ^2 from observed and expected frequencies. The *p*-value was calculated from the χ^2 distribution, to test the calibration of the logistical model. If the *p*-value of H-L test is >0.05, the analysis would fail to reject the null hypothesis that there is no difference, implying that the model's estimates fit the observed data at an acceptable level. Calibration was also assessed by plotting average observed versus average predicted outcome for each decile respectivly on the x and y-axes. Then, using a logistic regression model to obtain two derivatives: the slope and intercept. The slope, as a coefficient of the logit of predicted probability, represents the degree of variation in prediction. For a perfect model, the slope is equal to 1. The intercept, as a measure of overall calibration, indicates whether the predictions are systemically too low or too high. This indication should ideally be zero.

Discrimination refers to the ability of a model to separate subjects with and without the outcome of interest.[66] It can be quantified by the area under the receiver operating characteristic curve (AUC) and 95% confidence interval (CI). An AUC <0.5 is considered to represent a non-discriminative model, whereas an AUC >0.7 is considered to represent adequate discriminative ability by the model and an AUC >0.8 is excellent performance.[75] All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software from IBM (version 25.2; Chicago, Illinois).

RESULTS

Demographics and clinical characteristics

A total of 550 patients with severe TBI were enrolled in the BEST-TRIP study and an observational study conducted simultaneously. However, data from 466 (85%) TBI patients followed for six months or until death were included in the analyses. The patient characteristics are summarized in Table 1. The majority of this patient population were men (85.8%) with median age of 28 years (21-43); of these, 94.2% were younger than 65 years old. Only 4.4% reported drinking alcohol excessively within a month before the injury. At hospital admission, the proportion of patients with GCS motor score of 1 or 'No motor response' was 8.4%. The median GCS was 7, with 30.5% of subjects being intubated and 20.2% receiving sedation. One or both pupils were nonreactive in 16.4% of participants. Regarding the AIS score, 18.2% of the patients had major extracranial injury. The initial CT results revealed 20.3% had epidural hematoma (EDH) and 63.5% had subarachnoid hemorrhage (SAH). The results for clinical outcome for mortality at two weeks was 26%, at 6-months showed 48% of the participants had unfavorable outcome and 38% died.

The participant characteristics were summarized in Table 1 and were compared with the IMPACT and CRASH databased. Because the original dataset for CRASH also included mild TBI, therefore, we used the data from Roozenbeek and colleagues[76] where information from a subgroup of 6,681 patients from HICs and LMICs with moderate and severe TBI were obtained. The distribution of the GOS score for both the IMPACT and CRASH development datasets was U-shaped. This character was also found in our South American dataset. However, in our dataset, the proportion of subjects with SAH and EDH was higher: 63.5% SAH and 20.3% EDH, compared to 45% and 13% in the IMPACT dataset and 36% of SAH in the CRASH dataset (the presence of EDH was not collected in the CRASH study). The patients in the South America study also had a higher proportion of had severe brain pathology according to the Mashall score for CT findings. Moreover, we found that our data had a lower incidence of MEI, hypoxia, and hypotension compared to the IMPACT and CRASH datasets.

Table 1. Patient characteristics of South America, IMPACT, and CRASH datasets

Variables	South America N = 466	IMPACT N = 8509	CRASH N = 6681
Study design	RCT + Obs	RCT + Obs	RCT
Inclusion period	2008-2012	1984-1997	1999-2004
Age (year)			
Median (IQR)	28 (21-43) years	30 (21-45) years	32 (23-47) years
Male – no.(%)	472 (85.8%)	NA	NA
GCS post-resuscitation			
Severe (3-8)	100%	82%	39.5%
Median (IQR)	7 (5-8)	NA	NA
Motor score post-resuscitation – no.(%)			
None	39 (8.4%)	1395 (16%)	785 (12%)
Extension	45 (9.7%)	1042 (12%)	515 (8%)
Abnormal flexion	50 (10.7%)	1085 (13%)	658 (10%)
Normal flexion	69 (14.8%)	1940 (23%)	1156 (17%)
Localizes/obeys	144 (14.8%)	2591 (30%)	3567 (53%)
Untestable or missing	119 (25.5%)	456 (5%)	0
One or both pupils nonreactive – no.(%)	90 (16.4%)	2640 (37%)	1316 (20%)
Unequal pupil diameter – no.(%)	211 (38.4%)	NA	NA
Intubation – no.(%)	142 (30.5%)	NA	NA
Sedation – no.(%)	94 (20.2%)	NA	NA
Major extracranial injury – no.(%)	85 (18.2%)	NA	1735 (27%)
Marshall CT classification – no.(%)			
Diffuse injury I	7 (1.5%)	360 (7%)	954 (17%)
Diffuse injury II	71 (15.2%)	1838 (35%)	1517 (27%)
Diffuse injury III	160 (34.3%)	863 (17%)	604 (11%)
Diffuse injury IV	33 (7.1%)	187 (4%)	133 (2%)
Evacuated mass lesion (V) and Nonevacuated mass lesion (VI)	195 (41.8%)	1944 (38%)	2446 (43%)
Traumatic subarachnoid hemorrhage – no.(%)	345 (63.5%)	3313 (45%)	2045 (36%)
Epidural hematoma– no.(%)	110 (20.3%)	999 (13%)	NA
Hb (mg/dL)			
Median (IQR)	12 (11-14) mg/dL	13 (11-14)	NA
Anemia (Hb < 8 mg/dL)	21 (4.5%)	NA	NA
Glucose level (mmol/L)			
Median (IQR)	7.8 (6.6-9.5) mmol/L	8.2 (6.7-10.4) mmol/L	NA
Hypoglycemia (Glucose < 80 mg/dL)	7 (1.5%)		
Hyperglycemia (Glucose < 180 mg/dL)	70 (15%)		
Oxygen saturation (%)			
Median (IQR)	99 (97-100) %		
Hypoxia – no.(%)	4 (0.9%)	1116 (20%)	
Systolic Blood Pressure (mmHg)			
Median (IQR)	120 (106-132) mmHg		
Hypotension – no.(%)	32 (6.9%)	1171 (18%)	
Hypertension – no.(%)	7 (1.5%)		
6-month GOS			
Dead (1)	177 (38%)	2396 (28%)	2146 (32%)
Vegetative state (2)	10 (2.1%)	351 (4%)	993 (15%)
Severe disability (3)	77 (16.5%)	1335 (16%)	171 (12.1%)
Moderate disability (4)	62 (13.3%)	1666 (20%)	1224 (18%)
Good recovery (5)	140 (30%)	2761 (32%)	2318 (35%)
Median (IQR)	3 (1-5)	NA	NA
14-day mortality rate – no. (%)	122 (26%)	NA	1902 (19.5%)*
6-month GOS unfavorable outcome – no.(%)	264 (48%)	4082 (48%)	3310 (59.1%)
6-month mortality rate – no. (%)	177 (38%)	2396 (28%)	2146 (32%)

*The 14-day mortality rate in the CRASH study was from the total of 10,008 participants where mild, moderate, and severe TBI were combined together.

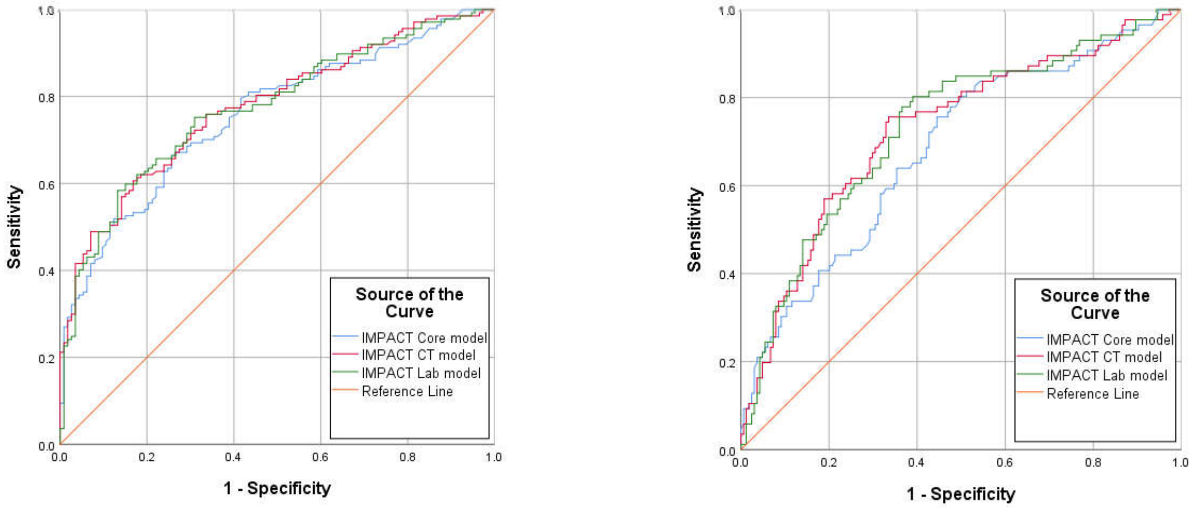
Model performance

The discriminative performance of all models was reasonable to accurately discriminate between favorable and unfavorable outcomes, as well as between survival and mortality (See Figure 1). The AUC values provided adequate levels of discrimination (AUC 0.683-0.775 for the IMPACT models, and AUC 0.640-0.731 for the CRASH models). When comparing the ability to predict unfavorable outcomes, the IMPACT CT model had the highest AUC. It is also shown that the IMPACT Lab model had the best discrimination for predicting 6-month mortality. Discrimination improved for both the IMPACT and CRASH models when the complexity of the models increased. These findings were in line with the improvement of prognostic strength when the ability to explain variability for each model was measured by Nagelkerke R^2. Other performance measures including the positive predictive value (PPV), negative predictive value, sensitivity, and specificity from the IMPACT and CRASH models were demonstrated in Table 2.

Table 2. Performance Measures of IMPACT and CRASH models

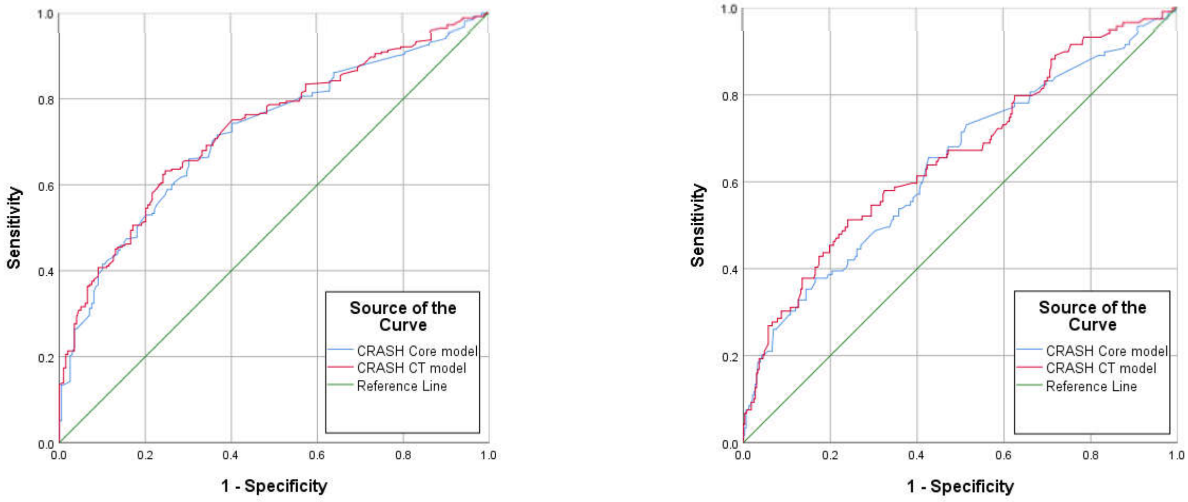
Performance Measures	IMPACT						CRASH			
	6-Month Unfavorable outcome			6-Month Mortality			6-Month Unfavorable outcome		14-day Mortality	
	Core	**CT**	**Lab**	**Core**	**CT**	**Lab**	**Core**	**CT**	**Core**	**CT**
Positive predictive value	72%	72%	72%	62%	65%	63%	70%	71%	82%	62%
Negative predictive value	65%	69%	69%	69%	72%	73%	63%	63%	75%	76%
Sensitivity	74%	77%	76%	36%	44%	36%	72%	71%	8%	13%
Specificity	64%	63%	64%	87%	87%	89%	60%	64%	99%	97%
AUC (95% CI)	0.756 (0.714-0.797)	0.775 (0.735-0.815)	0.772 (0.731-0.813)	0.683 (0.634-0.732)	0.726 (0.679-0.774)	0.731 (0.683-0.778)	0.718 (0.685-0.751)	0.731 (0.699-0.763)	0.640 (0.597-0.682)	0.661 (0.620-0.703)
Hosmer-Lemeshow test (p-value)	34.75 (0.000)	23.94 (0.002)	11.76 (0.161)	16.18 (0.040)	15.58 (0.049)	25.07 (0.002)	28.96 (0.000)	16.12 (0.041)	15.45 (0.051)	27.60 (0.001)
Nagelkerke R^2	0.24	0.30	0.29	0.16	0.21	0.18	0.19	0.21	0.07	0.11
Intercept	0.070	-0.013	0.114	0.075	0.028	0.046	0.174	0.171	0.102	0.069
Slope	1.009	1.147	1.041	0.984	1.081	1.053	0.880	0.984	0.760	1.053

Figure 1. AUC analysis comparing sensitivity and specificity of the IMPACT and CRASH models to discriminate unfavorable outcome and mortality



(A) AUC values for IMPACT models to predict unfavorable outcome at 6 months

(B) AUC values for IMPACT models to predict mortality at 6 months

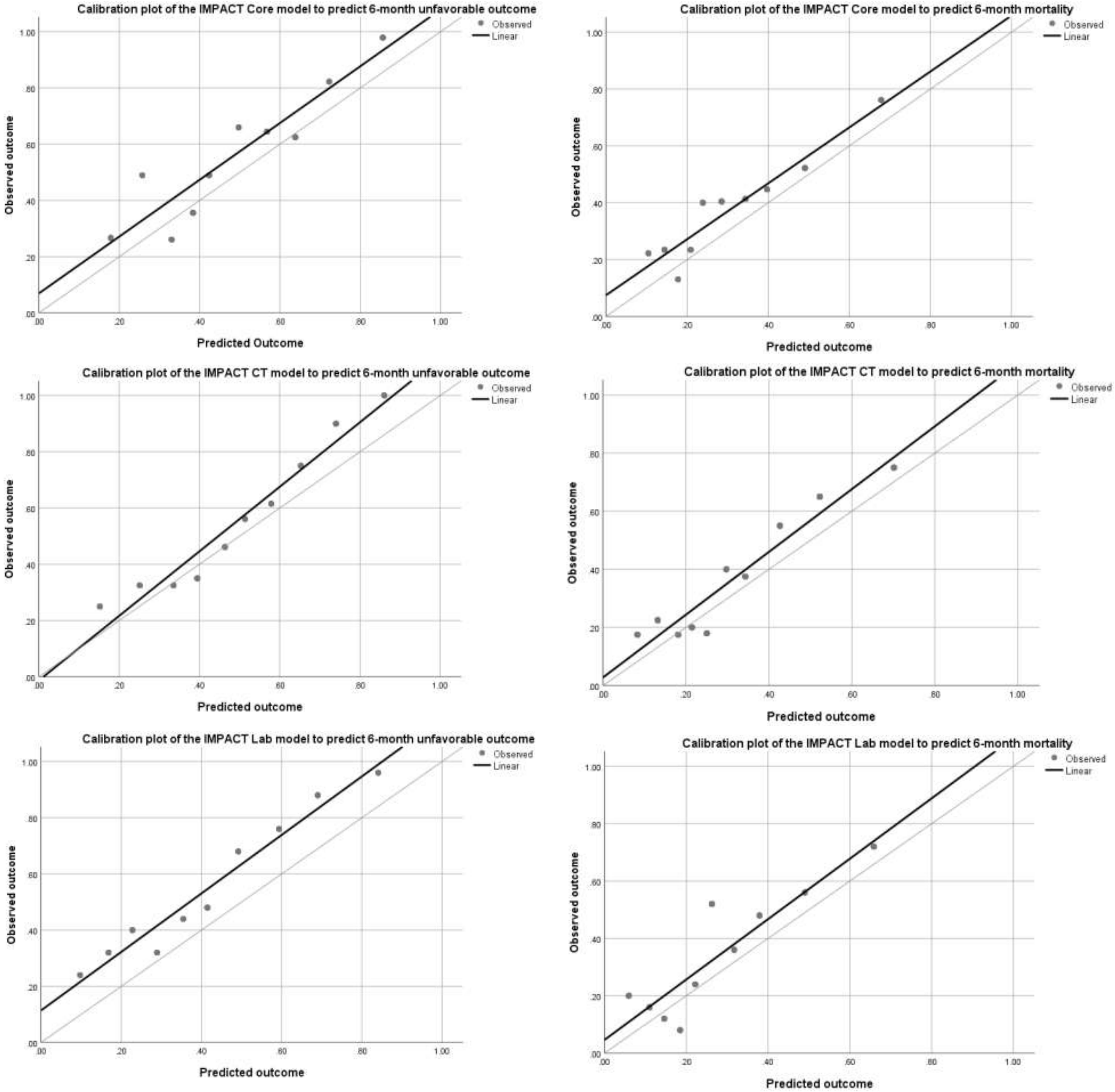


(C) AUC values for CRASH models to predict unfavorable outcome at 6 months

(D) AUC values for CRASH models to predict mortality at 14 days

The χ^2 analysis of the H-L test revealed that the IMPACT LAB model calibrated well when predicting 6-month unfavorable outcome, while the IMPACT CT and CRASH Core model calibrated well with mortality (p-values >0.05) (see Table 2). The calibration plots and intercept values indicated that the IMPACT and CRASH models, in general, predicted lower probabilities of both outcomes (disability and mortality) than that which were observed, except for the IMPACT CT model (see Figure 2 and 3). The IMPACT CT model would more accurately predict unfavorable outcome at 6 months only if the expected outcome is less severe. The slopes of the IMPACT models were close to 1 (range, 1.009-1.147) when predicting unfavorable outcome and mortality at 6 months, indicating a strong agreement between observed and predicted outcomes. Although the agreement between observed and predicted outcomes for the CRASH models was slightly lower than the IMPACT models, the slopes of the CRASH CT models were also close to 1 when predicting both 14-day mortality and unfavorable outcome at 6 months.

Figure 2. Calibration plots depicting observed versus predicted outcome for unfavorable outcome and mortality at 6 months for the IMPACT models (core, CT, and lab models)


Calibration plot of the IMPACT Core model to predict 6-month unfavorable outcome

Calibration plot of the IMPACT Core model to predict 6-month mortality

Calibration plot of the IMPACT CT model to predict 6-month unfavorable outcome

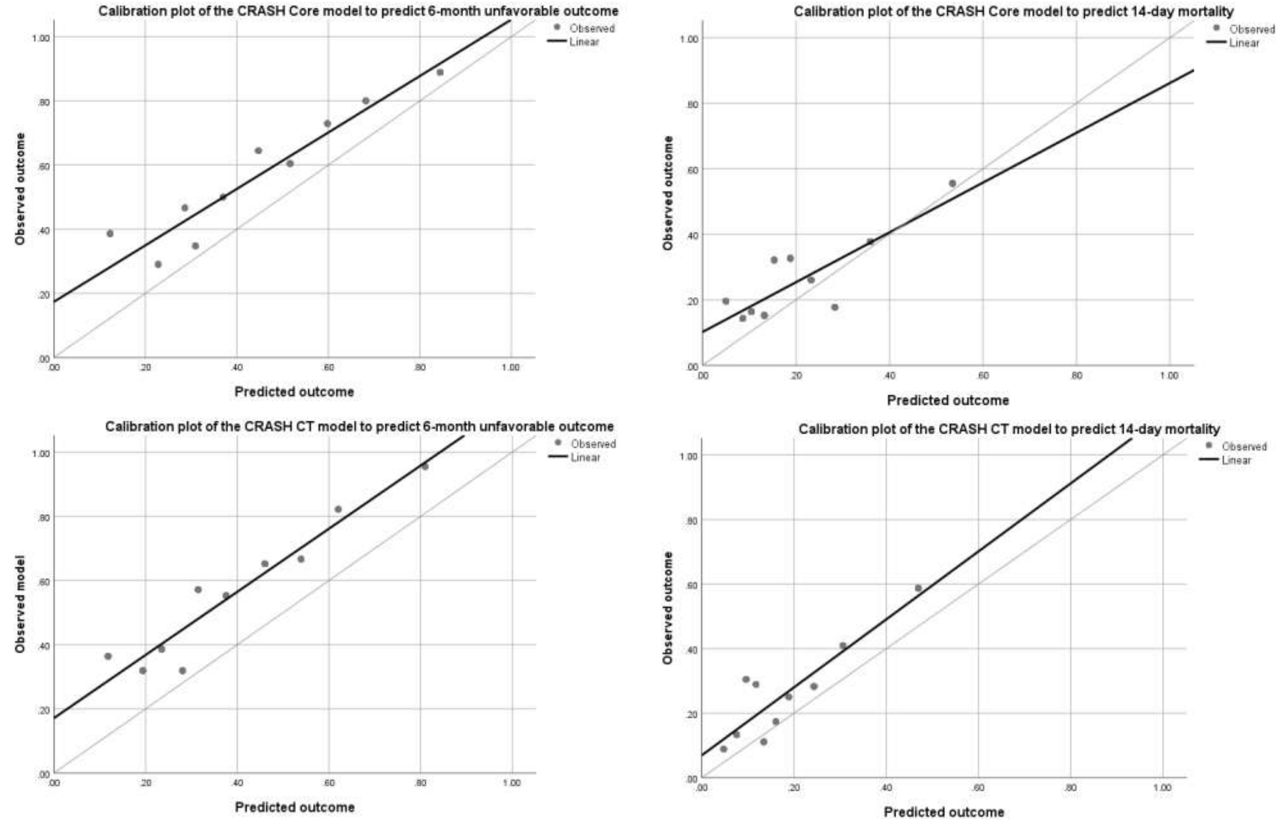
Calibration plot of the IMPACT CT model to predict 6-month mortality

Calibration plot of the IMPACT Lab model to predict 6-month unfavorable outcome

Calibration plot of the IMPACT Lab model to predict 6-month mortality

IMPACT Core model: age, motor score, pupil reactivity; IMPACT CT model: variables in the Core model plus hypoxia, hypotension, Marshall CT classification, subarachnoid hemorrhage, and epidural hematoma; IMPACT Lab model: variables in the CT model plus glucose and hemoglobin

Figure 3. Calibration plots depicting observed versus predicted outcome for unfavorable outcome at 6 months and 14-day mortality for the CRASH models (core and CT models)


Calibration plot of the CRASH Core model to predict 6-month unfavorable outcome

Calibration plot of the CRASH Core model to predict 14-day mortality

Calibration plot of the CRASH CT model to predict 6-month unfavorable outcome

Calibration plot of the CRASH CT model to predict 14-day mortality

CRASH Core model: Age, GCS score, pupil reactivity, major extracranial injury; CRASH CT model: variables in the Core model plus petechial hemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid hemorrhage, midline shift, nonevacuated hematoma

DISCUSSION

We conducted a study to externally validate five sets of prognostic models for predicting outcomes in patients with severe TBI using a dataset of 550 patients collected during 2008-2012 in South America. We focused on models that fulfilled high methodological standards in their development. The results from the external validation show that the overall performance of all IMPACT and CRASH models was adequate when used to predict outcomes in the dataset. The discrimination for both the IMPACT and CRASH models improved with the increasing complexity of the models. Calibration revealed that the IMPACT and CRASH models, in general, predict lower probability for unfavorable outcome and mortality than was observed.

The AUC and Nagelkerke R^2 indicated similar performance of the IMPACT CT and Lab models when used to predict 6-month unfavorable outcome, but the IMPACT lab model was the most accurate among all the models when used to predict 6-month mortality in the South American population. As the CT model includes more variables into the model (variables reflecting the secondary insults (hypoxia and hypotension), presence of structural abnormalities as visualized by CT scanning (Marshall CT classification, traumatic subarachnoid hemorrhage, and epidural mass) as well as the Lab model contains underlying pathophysiologic process (glucose level and hemoglobin); the combination of these variables results in the models with greater predictive ability.[15 77 78]

Our sample showed some differences in comparison with both CRASH and IMPACT models, as we have noted before. On average, patients in the current sample had less hypoxia and hypotension, but a higher incidence of SAH and EDH as well as higher Marshall score. We think these differences are related to the changing epidemiology of TBI.[1 66] The period of study for the IMPACT and CRASH datasets is around two decades before our dataset. Also, the evolution of CT imaging has also improved over this time period, which may have resulted in higher accuracy of CT findings. The differences in our patient characteristics were also reflected in calibration plots showing there were variations that could not be explained by the IMPACT and CRASH models. However, unless we combine the data from the IMPACT and CRASH studies to our dataset and perform a case-mix analysis for model calibration, we cannot confirm whether the poor calibration on external validation is attributable to case-mix effects.

The IMPACT and CRASH models had been extensively validated in four observational studies conducted recently including 1) the prospective cohort study of severe TBI dataset of 587 cases in the US [46], 2) the prospective cohort study using the national Neuroscience Institute data of 300 cases in Singapore [44], 3) dataset of 137 elderly patients with severe TBI from the retrospective cohort study in China [53], and 4) the retrospective data of 229 moderate and severe TBI conducted in Java [52]. All four studies concluded that the models show good performance on the validation datasets. The CRASH CT model was the most accurate among all the models when used to predict early mortality (14 days) [44 52], and the IMPACT lab model was the most accurate to predict 6 months mortality and unfavorable outcome [44 46 53]. However, the IMPACT models had poorer calibration, with an underestimation of mortality and unfavorable outcome when applied to the elderly population [53]. Our findings supported the previous study that the IMPACT and CRASH CT models are adequate when used to predict outcomes in patients with severe TBI. The IMPACT CT model is better to predict 6-month unfavorable outcome, and the IMPACT lab model for 6-month mortality.

Many studies have suggested the CRASH models are preferred when the population under study includes patients from LMICs [15 25 76]. Since the development population for the CRASH models included a substantial number of patients from LMICs [23], while the IMPACT models were developed mostly from the population in HICs [8]. Also, the CRASH models have major extracranial injury (MEI) as a predictor. The presence of MEI had a strong prognostic effect noted in patients with severe TBI. However, in our study where the data were collected from LMICs like Bolivia and Ecuador, the performance of the IMPACT models was superior to the CRASH models, especially when predicting mortality. We also found that the added prognostic effect of MEI in our dataset was negligible.

To explain which model is favored for our population, we considered the best values of calibration and discrimination after rigorous analysis. Calibration for both IMPACT and CRASH models revealed that they predicted lower probability for unfavorable outcome and mortality than that which were actually observed (Figure 3). Although the IMPACT CT and lab models showed good AUC and R^2 values to predict outcome in a group level; the sensitivity, specificity, PPV, and NPV did not appear to have enough impact on predicting outcome in an individual level (Table 2). In conclusion, the IMPACT models may be useful for quantifying the severity of brain injury for research studies. But the models were inadequate to apply in individual patients as a tool to provide realistic information to relatives on expectations of outcome or as an indicator to guide treatment resource allocation.

Our findings contribute further to the evidence base on the performance of prognostic models for severe TBI patients. The strength of this study is that our dataset included patient information from both observational study and clinical trials, thus permitting conclusions on generalizability.[66] However, the BEST-TRIP trial was not designed for predicting the outcome after TBI based on patients admission characteristics. Therefore, some important admission characteristics were missing included GCS and motor response.

When interpreting the results of this study, it is important to understand its limitations. Prognostic models should be seen as tools to predict outcomes in clusters of patients with certain characteristics and may thus aid clinical, research and policy work. The findings from this study inherit these characteristics, and they should be interpreted and used in such context. Additionally, prognostic models require continuous updating by including new predictors as developments continue in advanced brain imaging or the use of biomarkers for brain damage. Future external validation will be necessary due to the changing epidemiology of patients, the reorganization of trauma centers and treatment policies, and new approaches to outcome assessment with more complex features to reflect patient recovery.

CONCLUSION

External validation of prognostic models is important for reliable application of these model outside their own development settings. Although the IMPACT and CRASH models were developed on patients recruiting between 1985 – 2004, our findings that the discriminative performance is still reasonable in the dataset of the contemporary clinical studies indicate their continuing relevance. Overall, the discrimination for all IMPACT and CRASH models was adequate when used to predict outcomes in the South America dataset. The IMPACT CT and Lab models are the ones that present a higher discriminative capacity. However, some disagreement in calibration compared with the development population may have been caused by the effect of differences in patient characteristics between the developing dataset and validation dataset. Future investigations should explore case-mix effects. The IMPACT and CRASH models were more preferable to used in a group level as a stratification tool for research studies, rather than guiding patient care in an individual level. The findings from this study illustrate the necessity for updating prognostic models to maintain currency and generalizability.

SUPPLEMENTAL CONTENT

Appendix 1

Variables included in the IMPACT and CRASH prediction models

	Study population	Start of treatment	Core model	CT model	Laboratory model	Predicted outcome
IMPACT	GCS 3-15	≤4 – 24 h	Age, motor score, pupil reactivity	Core model plus: hypoxia, hypotension, Marshall CT classification, tSAH, and EDH	CT model plus: glucose and hemoglobin	Mortality or unfavorable outcome (GOS 1-3) at 6 months
CRASH	GCS ≤14	≤8 h	Age, GCS score, pupil reactivity, major extracranial injury	Core model plus: petechial hemorrhages, obliteration of the third ventricle or basal cisterns, SAH, midline shift, nonevacuated hematoma		Mortality at 14 days or unfavorable outcome (GOS 1-3) at 6 months

IMPACT, International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury; CRASH, Corticosteroid Randomization after Significant Head Injury; GCS, Glasgow Coma Scale; tSAH, traumatic subarachnoid hemorrhage; EDH, epidural hematoma; GOS, Glasgow Outcome Scale.

Appendix 2

Glasgow Outcome Scale (GOS) and Extended Glasgow Outcome Scale (GOSE) applied from [79]

	GOS		**GOSE**
5	Good recovery (GR)	8	Upper (GR+)
		7	Lower (GR-)
4	Moderate disability (MD)	6	Upper (MD+)
		5	Lower (MD-)
3	Severe disability (SD)	4	Upper (SD+)
		3	Lower (SD-)
2	Vegetative status (VS)	2	Vegetative status (VS)
1	Death (D)	1	Death (D)

Appendix 3

Marshall computed tomographic classification [72]

Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology is seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0-5 mm and/or lesions densities present; 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
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High or mixed density lesion >25 cm^3; not surgically evacuated

CT, computed tomographic

Appendix 4

Logistic regression coefficients and intercepts of the validated IMPACT models retrieved from IMPACT Prognostic calculator: http://www.tbi-impact.org/?p=impact/calc

	IMPACT Models					
	6-month Mortality			**6-month Unfavorable Outcome**		
	Core	***Extended***	***Lab***	***Core***	***Extended***	***Lab***
Intercept	-3.109	-3.787	-3.184	-2.644	-3.023	-2.470
Age	0.0342	0.0321	0.0204	0.0376	0.0332	0.0288
GCS motor=1	1.447	1.205	0.965	1.393	1.218	1.105
GCS motor=2	1.397	1.207	1.109	2.078	1.852	1.801
GCS motor=3	0.797	0.746	0.778	1.266	1.185	1.186
GCS motor=4	0.390	0.313	0.310	0.632	0.575	0.548
GCS motor=5/6	Ref	Ref	Ref	Ref	Ref	Ref
GCS motor=NA	0.522	0.425	0.462	0.885	0.837	0.059
Two pupils reactive	Ref	Ref	Ref	Ref	Ref	Ref
One pupil reactive	0.514	0.334	0.090	0.592	0.442	0.201
None pupil reactive	1.239	0.970	0.533	1.216	1.003	0.712
CT Class=1		Ref	Ref		Ref	Ref
CT Class=2		-0.298	-0.150		-0.530	-0.567
CT Class=3/4		0.774	0.715		0.543	0.508
CT Class=5/6		0.651	0.807		0.497	0.571
tSAH		0.606	0.740		0.567	0.666
EDH		0.379	-0.510		-0.572	-0.687
Hypoxia		0.237	0.360		0.316	0.396
Hypotension		0.667	0.366		0.614	0.440
Glucose (mmol/L)			0.097			0.085
Hemoglobin (g/dL)			-0.086			-0.092

GCS=Glasgow Coma Scale; CT Class=Marshall CT Classification; tSAH=traumatic subarachnoid hemorrhage; EDH=Epidural hematoma

Appendix 5

Logistic regression coefficients and intercepts of the validated CRASH models retrieved from CRASH Prognostic calculator: http://www.crash.lshtm.ac.uk/Risk%20calculator/index.html

	CRASH models			
	14-day Mortality		**6-month Unfavorable Outcome**	
	Basic	***CT***	***Basic***	***CT***
Intercept	-4.8450	-4.6603	-3.9887	-3.9323
Age (per year after 40 years)	0.0437	0.0453	0.0677	0.0697
Total GCS (per decrease in each unit variable is 17-total GCS score)	0.3322	0.2429	0.3529	0.2914
One pupil reactive	0.6599	0.3749	0.7155	0.4443
Two pupils reactive	1.3465	1.1389	1.5093	1.2726
MEI	0.1765	0.0759	0.5540	0.4655
Petechial hemorrhages		0.2275		0.3946
Obliteration of the third ventricle		0.6897		0.4281
tSAH		0.2845		0.1807
Midline shift > 5 mm		0.5834		0.6944
Non evacuated hematoma		0.3878		0.4794

GCS=Glasgow Coma Scale; MEI=major extracranial injury; tSAH=traumatic subarachnoid hemorrhage

Appendix 6

Data missingness

Variables	**% Missingness - n (%)**
Age (year)	4 (0.9%)
Male	5 (0.9%)
GCS post-resuscitation	12 (2.6%)
Motor score post-resuscitation	119 (25.5%)
One or both pupils nonreactive	121 (22%)
Unequal pupil diameter	2 (0.4%)
Intubation	6 (1.3%)
Sedation	9 (1.9%)
MEI	0
Marshall CT classification	0
Hb (mg/dL)	93 (20%)
Glucose level (mg/dL)	144 (30.9%)
Oxygen saturation (%)	38 (8.2%)
Systolic Blood Pressure (mmHg)	30 (6.4%)
6-month GOS	84 (15.3%)

CHAPTER 4: Validation of a Prognostic Model for Outcome after Severe Brain Injury Based on Patient Admission Characteristics in a Thai Cohort

Title: Validation of a Prognostic Model for Outcome after Severe Brain Injury Based on Patient Admission Characteristics in a Thai Cohort

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Keywords: severe traumatic brain injury, validation, prognostic model, mortality, Glasgow outcome scale, low and middle-income countries

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Abstract

Background: Most traumatic injuries occur in low and middle-income countries, but few outcome prediction models have been developed using these populations. This study aims to create an accurate and reliable model for predicting outcome following traumatic brain injury (TBI) that clinicians in Thailand and other limited resource settings can use to assist in clinical decision making, guide prognostic discussions with patients' families, and conduct future research.

Setting: A level I trauma center at Budhachinaraj Phitsanulok Hospital, Thailand.

Participants: Patients older than 13 years old with blunt TBI; admitted to the hospital within 24 hours of injury; had GCS $\leq$8 (with the GCS motor component of 1-5 if the patient was intubated) or a higher score on admission that dropped to the specified range within 48 hours after injury; that were admitted to the Emergency Department (ED) of the study hospital between January 1, 2015 and December 31, 2017.

Design: Retrospective cohort study.

Measures/Methods: Data extraction from medical records of eligible subjects was performed.

Two models were developed using multivariate logistic regression methods for predicting in-hospital death and early functional outcome at 1-month after injury using Glasgow Outcome Scale (GOS). Poor early functional outcome was defined as GOS $\leq$3. Bootstrap technique was performed for internal validation. Then variables used in the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) and Corticosteroid Randomization after Significant Head Injury (CRASH) core models were used to compare the model performance with the newly developed Thai models.

Results: Patient pre-injury comorbidity, anisocoria, glucose level and motor response post-resuscitation were independent predictors of in-hospital mortality. For functional outcome measured by GOS, respiratory rate at hospital admission, hematocrit, and Glasgow Coma Scale (GCS) score post-resuscitation were independent predictors. The AUC measures for discrimination ability of all models in the present study are comparable with other models in the literature (AUCs range from 0.730-0.807). For in hospital death, the Thai model for mortality, the set of variables in IMPACT and CRASH models showed good calibration (Hosmer-Lemeshow test *p*-value >0.05). However, when predicting GOS outcome, there were some disagreements between observed and predicted outcomes in the Thai model for unfavorable outcome and the variables in IMPACT model.

Conclusion: The Thai models possess good discriminative ability for prediction of 1-month unfavorable outcome and mortality in patients with severe TBI. Because the data used in the present analysis came from a single site, future external validation should be conducted to confirm model generalizability before applying them more broadly in patients with severe TBI in LMICs.

Keywords: severe traumatic brain injury, validation, prognostic model, mortality, Glasgow outcome scale, low and middle-income countries

BACKGROUND

Traumatic brain injury (TBI) is a major cause of death and disability throughout the world. Approximately 69 million individuals sustain a TBI each year, and most (56%) of those TBIs result from road traffic collisions in low- and middle-income countries (LMICs) in Africa and Southeast Asia.[80] Despite increased attention to development of therapeutic targets and agents, at present, TBI has no specific therapy to address the primary injury and improve patient outcomes.[81] Hence, patient care is geared toward initiating therapeutic strategies to prevent and minimize factors that extends initial brain damage, called secondary brain injury, as soon as possible.[34]

To provide optimal clinical TBI management, clinicians have to weigh risks and benefits of an intervention considering individual patient prognosis. Accurate and reliable prognostic models for TBI are necessary to improve clinical decision making, resource allocation, and stratification as well as utilizing findings from randomized controlled trials (RCTs).[63] Several prognostic models for TBI have been available for decades, but none are widely used in clinical practice.[12] Reasons for lack of clinical translation include that many of these models were developed from small samples of patients, had poor methodology, were rarely externally validated, and were not clinically practical.

Currently, the most well established prognostic models for TBI came from two databases: the International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT)[23] and the Corticosteroid Randomization After Significant Head Injury (CRASH) trial.[82] Both databases were developed on large patient samples from multiple countries and have been externally validated.[44 83] While the data to support the development of the IMPACT models was collected in high-income countries (Netherlands, United Kingdom, and the United States) during 1984 and 1997;[23] the CRASH models were developed from data collected in 1999-2004 with a high percentage of patients coming from low and middle-income countries.[84] Predictors used in the IMPACT core model include age, Glasgow Coma Scale (GCS) motor score, and pupillary reactivity. The CRASH basic model includes age, GCS, pupillary reactivity, and presence of major extracranial injury. Although it is reasonable that biologically the prognostic factors should be the same for all patients, however, the association can differ by geographic location and evolve over time.

Thailand is a middle-income country that has a high mortality rate of TBI from road traffic crashes.[85] Thailand has resource limitations that make TBI management more challenging than other countries due to longer pre-hospital times, non-specialist transport personnel, limited availability of neurotrauma-focused intensivists, and a limitation in availability of intracranial pressure monitoring technology. Thus, it may be inappropriate to extrapolate models from high-income countries for use in settings such as Thailand. In this study, we aim to compare the performance of a new prognostic model with the set of variables in IMPACT and CRASH Core models using available data on patient admission for hospital death and early functioning outcome at 1-month after injury in patients with severe TBI. Our goal is to create an accurate and reliable instrument for predicting outcome from TBI that TBI clinicians in Thailand, and perhaps other limited resource settings, can use to assist in clinical decision makings, guide prognostic discussions with patient families, and conduct future research.

MATERIALS AND METHODS

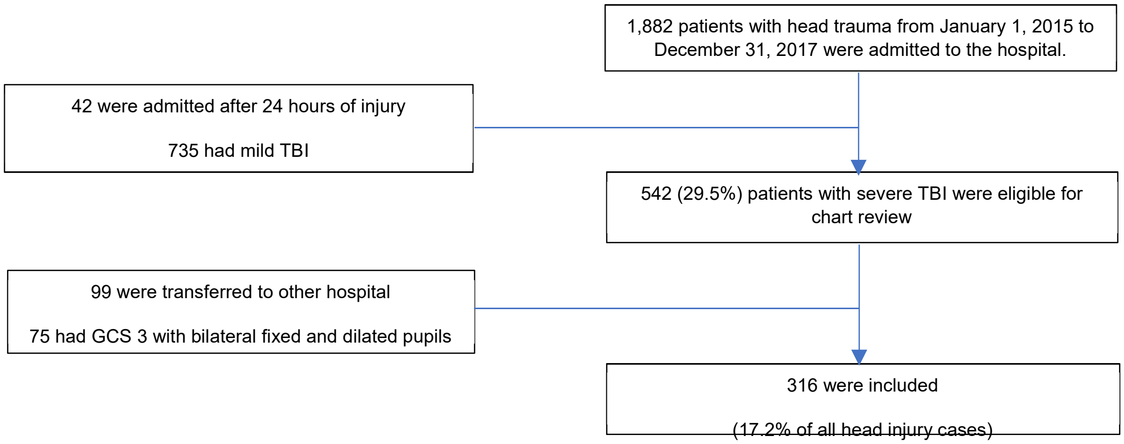
Design, patients and samples

This is a retrospective cohort study using medical record review conducted in a level I trauma center at Budhachinaraj Phitsanulok Hospital, Thailand. The hospital has intensive care unit (ICU) bed capacity range up to 12 beds covered by the neurosurgical or intensivist team 24 hours a day. The standard management for severe TBI includes vital sign monitoring and neurological assessment, cardiopulmonary maintenance, early enteral feeding, and the management of complications related to neurologic alteration including hyperthermia, hypo-/hyperglycemia, and seizure. Intracranial pressure (ICP) monitoring is not common in this unit because of resource limitation, and the decision to provide such monitoring depends solely on individual neurosurgeon judgment.

All patients admitted to the Emergency Department (ED) between January 1, 2015 and December 31, 2017 with a diagnosis of TBI due to blunt injury were screened for eligibility for this study. Patients were eligible based on the following study inclusion criteria: 1) admitted to the hospital within 24 hours of injury, 2) GCS $\leq$8 (with the GCS motor component of 1-5 if the patient was intubated) or a higher score on admission that dropped to the specified range within 48 hours after injury, and 3) age $\geq$13. Patients were excluded if they had GCS score of 3 and bilateral fixed and dilated pupils at the time of admission. Study protocol was carried out in accordance with the Declaration of Helsinki and was approved by the Human Subjects Division, University of Washington and the study hospital's Ethical Review Board.

Subject characteristics were obtained via medical record review including demographics (age, gender), comorbidity measured by Charlson Comorbidity Index (CCI),[86] severity of clinical condition (GCS and pupillary response at admission, heart rate, respiratory rate, blood pressure, body temperature), selected laboratory test results at admission (levels of glucose, hematocrit, platelet count, and coagulation as prothrombin time (PT) and activated partial thromboplastin time (aPTT)), as well as injury severity that was determined using Injury Severity Score (ISS).[87] In the present study, the ability of the models to predict two outcomes, hospital mortality and the Glasgow Outcome Scale (GOS)[88] at 1-month after injury, were assessed.

Figure 1. Study Screening and Eligibility



Statistical analysis

Descriptive analyses were implemented using qualitative variables that were represented in the tables as absolute frequencies and percentages. Quantitative variables were expressed using mean and standard deviation or median and interquartile range (IQR), depending on their clinical meaning and whether or not they followed a normal distribution. GOS was handled as a dichotomous variable for analyses. An unfavorable outcome was defined as GOS $\leq$3 (dead, vegetative state, or severe disability), and a favorable outcome as GOS 4-5 (moderate disability or good recovery) as well as patients as having died (GOS 1) or survived (GOS 2-5). Multiple imputation used as an approach to handle missing data of the predictors.

Development of a Predictive Model

We focused on accurate estimation of the perfomance of a predictive model based on the full sample. We applied stepwise selection with forward method to identify predictors from the full set of possible variables. Once the model was determined, the bootstrap technique was used for the most effective validation.[22]

Comparing predictive performances between the Thai models with the set of variables in IMPACT and CRASH Core models

We measured the newly developed model's performance against the set of variables in the IMPACT and CRASH core model performance for discrimination and calibration. Discrimination refers to the ability to distinguish high-risk subjects from low-risk subjects and is commonly quantified by a measure of concordance or the *c*-statistic. For this study, we used binary outcomes. Thus the *c*-statistic is identical to the area under the receiver operating characteristic (AUC) curve. The *c-statistic* varies between 0.5 and 1.0 for sensible models, where the higher *c-statistic,* the better. Other performance measures included positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were also used to assess the model discrimination as well. Calibration evaluates whether the predicted probabilities agree with observed probabilities.[21] Calibration was assessed with the Hosmer-Lemeshow (H-L) goodness of fit test.

RESULTS

Demographics and outcomes

A total of 316 patients met the inclusion criteria and were included in the present study (see Figure 1 for the algorithm of the study). Table 1 shows the patient demographics and clinical characteristics. The mean age was 46 years and most of the subjects were men (82.6%). The majority of subjects were healthy or had history of mild illness (CCI = 0-2). Motor vehicle crash (67.4%) followed by fall (14.2%) were the most common causes of injury. More than 70% of patients were transfers with the average time interval from injury to arrival at the study hospital being 5 hours. Although the sample only included those with severe TBI, GCS at ED admission varied from 3-15. Most subjects (81%) were intubated and provided with ventilator support during their admission. We found that 52.2% died at the hospital. At one-month after injury, 7.9% were readmitted with complications following TBI, and 80% of subjects had unfavorable outcome as assessed by GOS. The p-values for distribution of each characteristic between GOS favorable outcomes and unfavorable outcomes were signified in Table 2.

Table 1. Demographic data and health status at ED admission (N = 316 patients)

Characteristics	Frequency (%) or Mean (±SD) or Median (IQR)	Range	Missing data (%)
Age (years)	46 (19)	15 - 96	10 (3.2%)
Male	261 (82.6%)		0 (0%)
Married	190 (60.1%)		7 (2.2%)
Educational level			0 (0%)
None	18 (5.7%)		
Elementary	154 (48.7%)		
Junior High School	45 (14.2%)		
Senior High School	40 (12.7%)		
Vocational Certificate	35 (11.1%)		
University	24 (7.5%)		
Employment			24 (7.6%)
Student	25 (7.9%)		
Employed	213 (67.4%)		
Unemployed	40 (12.7%)		
Unknown	14 (4.4%)		
Family support available	225 (71.2%)		10 (3.2%)
Charlson Comorbidity Index (CCI)		0-11	10 (3.2%)
0	176 (55.7%)		
Mild (1-2)	72 (22.8%)		
Moderate (3-4)	48 (15.2%)		
Severe (>5)	20 (6.3%)		
Mechanism of injury			15 (4.7%)
Motor vehicle crash	213 (67.4%)		
Assault	12 (3.8%)		
Fall	45 (14.2%)		
Other	31 (9.8%)		
Injury severity score (ISS)	20.7(8.2)	16 - 57	0 (0%)
Time from injury to the study setting ED (hours)	5 (6)	0.5 - 23	21 (6.6%)
Transferred from other hospital (cases)	246 (77.8%)		0 (0%)
Glasgow coma scale (GCS) at admission	6 (5-7)	3 - 15	0 (0%)
Pupil response			0 (0%)
Anisocoria	137 (43.4%)		
Cannot examine	17 (5.4%)		
Intubation	256 (81.0%)		60 (19%)
Surgery	159 (50.3%)		157 (49.7%)
Lab after hospital admission			
Platelet (μL)	204,779 (87,329)	18,000 – 548,000	6 (1.9%)
TP (sec)	20 (51)	9.6 – 600	18 (5.7%)
KPTT (sec)	36 (62)	17.1 – 600	18 (5.7%)
Hct (%)	35 (8)	8 – 61	4 (1.3%)
%Sat O2 (%)	98 (6)	20 – 100	26 (8.23%)
Glycemia (mg/dl)	174 (75)	29 - 574	60 (18.99%)
Glasgow coma scale (GCS) at ICU admission	6 (2)	3 - 6	0 (0%)
Outcomes			
Glasgow outcome scale (GOS)	1 (1-3)	1 – 3	3 (0.9%)
GOS unfavorable outcome	253 (80.1%)		3 (0.9%)
Rehospitalization	25 (7.9%)		0 (0%)
Death	165 (52.2%)		0 (0%)

Table 2. Clinical outcome and characteristics of the patients. All values are presented as mean (SD) except where noted.

Parameter	Favorable outcome (n = 60)	Unfavorable outcome (n = 253)	p-value
Age (year)	40 (16)	48 (19)	.001*
Length of hospital stay (day)	11 (9)	9 (11)	.203
Injury severity score	22 (9)	20 (8)	.269
Charlson Comorbidity Index (CCI)	1 (1)	1 (2)	.003*
Time from injury to ED	5 (5)	5 (6)	.893
Glasgow coma scale (GCS) at admission	7 (2)	6 (2)	.003*
Eye response at admission	1 (7)	1 (7)	.961
Motor response at admission	4 (1)	4 (1)	<.001**
Anisocoria at admission	18 (5.8%)	118 (37.7%)	.021**
Vital signs at hospital admission			
HR	97 (21)	98 (24)	.792
RR	23 (11)	21 (3)	.113
SBP	133 (24)	136 (34)	.518
DBP	82 (19)	81 (23)	.973
MAP	99 (20)	100 (25)	.802
Body temperature	37.0 (1.0)	37.0 (1.1)	.872
Lab after hospital admission			
Platelet µL	216,766	201,099	.214
TP sec	(73,754)	(90,362)	.231
KPTT sec	12.6 (2.5)	21.9 (57.4)	.000**
% Hct	23.9 (3.4)	40.0 (69.6)	.001**
%Sat O2	37 (6)	34 (9)	.432
Glycemia mg/dl	98 (3)	97 (6)	.199
	163 (51)	178 (80)	
Glasgow coma scale (GCS) post resuscitation	7 (2)	6 (2)	.000**
Eye response post resuscitation	2 (1)	1 (1)	.013*
Motor response post resuscitation	4 (1)	3(1)	.000**
Anisocoria post resuscitation	8 (2.6%)	30 (9.6%)	.753
Rehospitalization	9 (2.9%)	15 (4.8%)	.018*

***p<0.001, *p<0.05*

We performed forward-stepwise regression on the drawn 200 bootstrap samples of N = 316. The multivariate logistic regression analysis revealed that respiratory rate at hospital admission, hematocrit (Hct), and GCS post resuscitation were independently associated with GOS at 1-month after injury (Table 3a). However, none of these predictors were associated with the outcome of in-hospital mortality. Rather, comorbidity (measured by CCI), anisocoria, glucose levels, and motor response post resuscitation were independent predictors of in-hospital mortality. The difference of model performance for the GOS outcome calculated from the original sample C-statistics and the average bootstrap sample was 0.03 (C_{diff} = 0.752 - 0.722 = 0.03), and the C-statistics difference for the model predicting mortality was 0.19 (C_{diff} = 0.991 - 0.807 = 0.18). These values show that the developed model shows excellent calibration even after accounting for possible overfitting.[22] The association between selected predictors and study outcomes were demonstrated in Table 3a and 3b.

Table 3a. Association between predictors and hospital mortality

Parameter	GOS				
	B	SE	Wald	p	Odds Ratio (95% CI)
Constant	.202	.721	.078	.780	1.223
CCI	.232	.094	6.115	.013	1.262 (1.049 – 1.517)
Anisocoria	.816	.277	8.659	.003	2.262 (1.313 – 3.895)
Glucose levels	.006	.002	6.130	.013	1.006 (1.001 – 1.011)
Motor response post resuscitation	-.750	.121	38.530	.000	0.472 (0.373 - 0.598)

Table 3b. Association between predictors and 1-month GOS (favorable and unfavorable)

Parameter	GOS				
	B	SE	Wald	p	Odds Ratio (95% CI)
Constant	8.16	1.53	28.51	.000	3.489
RR	-0.11	0.05	4.42	.035	0.90 (0.81 – 0.99)
Hct (%)	-0.05	0.02	6.19	.013	0.95 (0.91 – 0.99)
GCS post resuscitation	-0.42	0.09	21.82	.000	0.66 (0.55 – 0.79)

Two prognostic models were developed for predicting GOS at 1 month and hospital mortality, respectively. The performance of these models compared to models built using the set of variables from IMPACT and CRASH core predictors is shown in Table 4. Hospital mortality was 52.2%. One-month unfavorable outcome was 80.1%. The Thai predicted death model explained 34% of the variance in hospital mortality and correctly classified 75.4% of cases. The PPV, sensitivity, and specificity indicated the Thai predicted death model was superior to the variables in the IMPACT and CRASH models for predicting in-hospital mortality (see Table 4). Overall, the discriminative ability of the Thai predicted death model was the highest among other compared models (AUC = 0.807, 0.768, and 0.768, respectively) (see Figure 2).

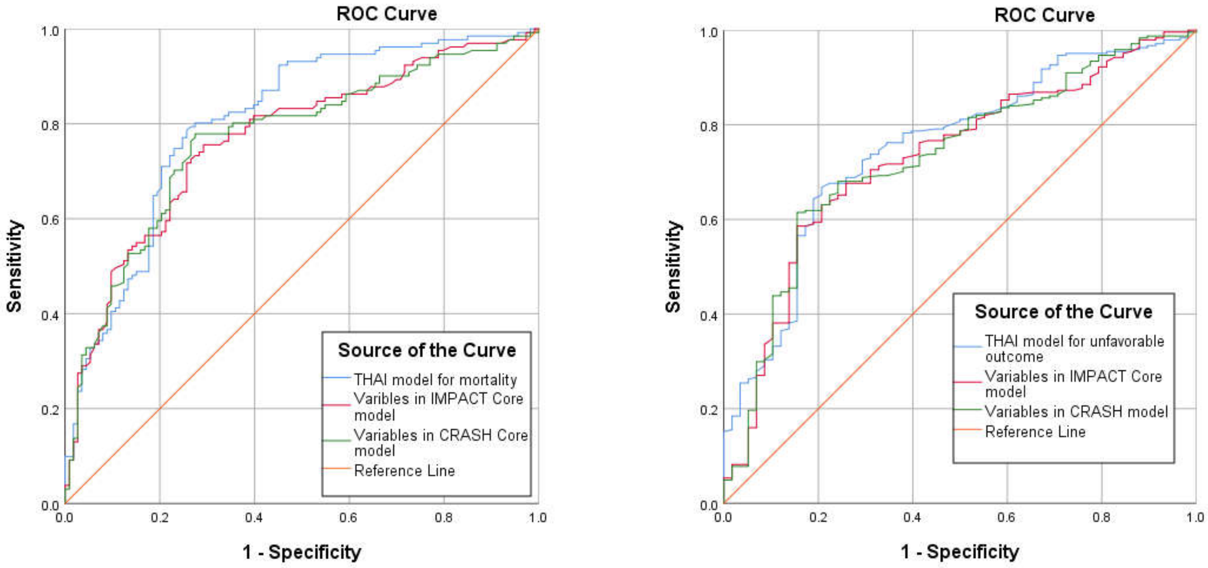
In contrast, the model which predicted GOS unfavorable outcome at 1 month only explained 18.6% of the variance and correctly classified 79.9% of cases. Although the AUC for the unfavorable outcome in the Thai model was higher compared to the variables in the IMPACT and CRASH models (AUC = 0.752, 0.730, and 0.732, respectively), its NPV and sensitivity were lower than the other models.

For in-hospital mortality outcome, calibration for the Thai model and the set of variables in CRASH model were good when evaluated with the H-L test (*p*-value >0.05), but poor in the set of variables in the IMPACT model. For 1-month GOS unfavorable outcome, the performance of the Thai model was not good in term of calibration. The comparison of performance between the Thai models versus the set of variables in the IMPACT and CRASH models are specified in Table 4.

Table 4. Performance Measures of the Thai model, IMPACT model, and CRASH model after accounting for possible overfitting using bootstrap sample

	Thai Model		Variables in IMPACT Core model		Variables in CRASH Core model	
	Hospital Mortality	1-month Unfavorable outcome	Hospital Mortality	1-month Unfavorable outcome	Hospital Mortality	1-month Unfavorable outcome
Positive predictive value	77%	82%	73%	82%	74%	82%
Negative predictive value	75%	40%	69%	67%	71%	54%
Sensitivity	80%	96%	70%	99%	72%	98%
Specificity	73%	10%	72%	7%	73%	12%
AUC (95% CI)	0.807 (0.752-0.862)	0.752 (0.685-0.820)	0.768 (0.708-0.827)	0.730 (0.659-0.800)	0.768 (0.708-0.828)	0.732 (0.662-0.802)
Hosmer-Lemeshow test (p-value)	10.752 (0.216)	17.512 (0.025)	19.272 (0.013)	11.836 (0.159)	10.926 (0.206)	14.429 (0.071)
Percentage correct	76.3%	79.9%	70.8%	81.4%	72.4%	81.1%
Nagelkerke R^2	35%	18.6%	25.4%	16.5%	24.5%	16.9%

Figure 2. AUC analysis comparing sensitivity and specificity of the Thai models vs. the set of variables from IMPACT and CRASH Core models to discriminate mortality (A) and unfavorable outcome (B)



(A) Mortality at 1 month

(B) Unfavorable outcome at 1 month

* To account possible overfitting, The AUC values were all based on bootstrap sample

Overall, for in-hospital mortality, the performance of the Thai predicted death model was better as compared to the set of variables from the IMPACT and CRASH models. The performance in predicting GOS unfavorable outcome was similar in all models. Therefore, the Thai model which includes patient comorbidity, clinical severity, and laboratory parameters has the highest discriminative ability to predict mortality and GOS unfavorable outcome at 1-month.

DISCUSSION

Using the patient admission data of patients with severe TBI from Budhachinaraj Phitsanulok Hospital, one of the largest level I trauma centers in Thailand, two prognostic models were developed and validated to predict the risk of in-hospital mortality and GOS unfavorable outcome at 1 month. We compared the performance of the new prognostic models with the set of variables in the IMPACT and CRASH core models, and finally, the best performing prognostic model was identified. All the prediction models had good discrimination in the Thai data set. Calibration of the Thai model and CRASH model to predict mortality was good, but the Thai model was poor in predicting GOS outcome. The AUC of TBI prediction models for mortality and unfavorable outcome in the literature varies from 0.50-0.89.[12] Table 4 shows the comparison of the performance measures of the newly developed Thai models versus the set of variables from IMPACT and CRASH Core model. The AUC values and Nagelkerke's R^2 for discrimination ability of all models in the present study are comparable with other models in the literature (AUCs range from 0.730-0.807). The Thai model for prediction of mortality performed better than variables in either the IMPACT or CRASH Core model. It is also proved to adequately perform to predict risk of unfavorable outcome compared to the IMPACT or CRASH Core models as well.

Although external validation is essential for generalizability (indicates how a model performs in new patients), the Thai models are based on bootstrapping validation and also smaller samples than that of the IMPACT and CRASH studies. The calibration of the Thai model and CRASH Core model to predict mortality was good (H-L test *p*-value >0.05), but there were some disagreements between observed and predicted GOS outcomes in the Thai model. This disagreement may be, in part, because calibration of the models is influenced by the effect of predictors and by the distribution of outcomes.[83] This study did not examine the extent to which these factors may contribute to the disagreements, and future analysis should determine whether the miscalibration was influenced by either potential source.

The multivariate logistic regression analysis revealed that comorbidity (measured by CCI), anisocoria, glucose levels, and motor response post-resuscitation were independent predictors of in-hospital mortality.

But for functional outcome measured by GOS, respiratory rate at hospital admission, Hct, and GCS post-resuscitation were independent predictors. Most of these independent predictors have previously been identified as prognostic factors for poor outcome in cases of TBI.[27 44 46 55 89-91] To date, there are increasing numbers of study linking comorbidities to TBI outcomes.[92-96] Our study also utilizes patient's comorbidity as an independent prognostic factor and supports its importance in predicting the in-hospital mortality. Information of comorbidity was assessed and collected for all patients by clinician in the emergency department or intensive care unit as a routine assessment. Easy availability of this variable at the study hospital and its clinical importance for in-hospital mortality were the main reason to examine this variable as a predictor.

Unlike other studies which have validated the IMPACT and CRASH model, this study did not include the prognostic information from the computed tomography (CT) scan.[23 44 46 53 56] This study was conducted in a middle-income country hospital where there is a limited number of radiologists and Marshall's CT classification is not usually implemented in review of head CTs. Thus, we decided not to include this variable in the analyses. However, information from CT imaging can help differentiate patients who require urgent or emergent neurosurgical intervention from those who can be safely monitored in ward.[64] Incorporating a CT scoring system in TBI (ex. Marshall CT classification) can be used to predict patient outcomes and to stratify patients in clinical trials.[60] A next step to improve generalizability and performance for the Thai models would be to include information from CT imaging, and then validate the Thai+CT models against the IMPACT and CRASH CT models.

Although the benefit of using laboratory variables in prognostic studies is that they are potentially modifiable,[65] such laboratory results at the ED admission have not been widely used after TBI.[12 66] Some studies in persons with TBI report the impact of laboratory parameters to be smaller than other well-known predictors;[12 13 77 90] this study, however, revealed that blood glucose level and hematocrit at ED admission were more associated with outcome following TBI than GCS or motor score after resuscitation. Anemia and hyperglycemia are frequent among TBI patients, where it has been associated with an increased risk of poor outcome.[97 98] However, many studies show that hemoglobin level below 9 g/dl was associated with poorer outcomes whereas the amount of red blood cell transfusion (RBCT) was also related to increase

ICU length of stay and mortality.[97 99] Also, no solid evidence exist that tight glycemic control improves outcome in TBI patients. On the contrary, it might lead to hypoglycemic episode with deleterious effect on the injured brain.[100] To date, there is insufficient evidence to provide strong recommendations regarding which hemoglobin or hematocrit level and glucose level to target and if such changes from baseline levels are associated with improved outcomes. Future studies are needed to explore an optimal and safe hemoglobin or hematocrit level and glycemic range and rate of change to facilitate critical care of anemia and blood glucose control.

Clinical severity in patients with TBI relates to both extracranial and intracranial injuries.[61] The ISS was consistently registered at the study hospital and included in the analyses. However, as every case sent to this tertiary care center had concomitant multiple injuries and was classified as severe TBI, thus there was little variability in the sample in ISS. In fact, all of them were considered having major extracranial injury (MEI). Thus, the additional predictive value of MEI may be small so that it was not included in final regression models. This may also have caused the CRASH model to perform worse than the Thai model; even though it has been externally validated and recommended for use with the LMIC TBI populations.

The prognostic value of vital signs in TBI has been underappreciated for a long time.[12 66] This study revealed that an increase in respiratory rate was a protective risk factor against unfavorable outcome after TBI. We did not have information whether the increase in respiratory rate was caused by ventilation therapies or it was the physiologic response to the injury. Also, the Guidelines for the Management of Severe TBI suggests that unless hyperventilation is unavoidable during the first 24 hours after injury; patient's oxygen delivery should be monitored using advanced technologies such as brain tissue O_2 partial pressure ($BtpO_2$).[101] This recommendation is not applicable to settings where high-technology monitoring is limited. Further study should be conducted to determine the relationship between respiratory rate and functional outcome after TBI.

Very few prognostic studies have been done in LIMCs.[47 48 52] This study is the first of its kind to develop and validate the models for a limited-resource population of patients with severe TBI in Thailand. However, the study has some limitations. First, the models were developed from a single-center data set and have not been validated externally. Further, our study hospital only had records of patient follow-up until a month after injury. Thus, the outcome measures for the Thai models were mortality and GOS outcome at 1 month, instead of 14-day or 6-month mortality and 6-month unfavorable outcome where both IMPACT and CRASH models performed well. Also, the models were developed from a retrospective data set; this might produce biases regarding patient characteristics, data collection, and analysis. Thus, there is a need for development and validation of models based on large patient population from multiple centers to enhance the models' generalizability. The strength of odd ratios reported in this study could be affected by patient characteristics in the Thai data set since the data was recruited from patients with severe TBI whose GCS mostly ranged from 5-7 at admission. Extrapolation of the model to predict outcome following mild or moderate TBI is not possible at this time.

CONCLUSION

Prognostic models with admission data are essential to support early clinical decision-making, and to facilitate reliable comparison of outcome between different patient series and variation in results over time. This study aims to create an accurate and reliable instrument for predicting outcome from TBI that clinicians in Thailand, and perhaps other limited resource settings, can use to assist in clinical decision making, guide prognostic discussions with patient families, and conduct future research. The Thai models possess good discriminative ability for prediction of 1-month unfavorable outcome and mortality in patients with severe TBI. Because the data used in the present analysis came from a single site, future external validation should be conducted to confirm model generalizability before applying them more broadly in patients with severe TBI in LMICs.

CHAPTER 5: Conclusion

Globally, the annual incidence rate of traumatic brain injury (TBI) in all ages is 349 per 100,000 person-years.[2] The incidence of TBI varies across regions, populations, regulations, and health systems; but in general, the rate is expected to be higher in low and middle-income countries (LMICs).[6] As LMICs usually have poor pre-hospital care, delays in patient transfer, lack of facilities and well-trained staff; these make the burden of TBI more devastating and a pressing public health issue.[7] In this dissertation, we focused on several approaches to determine the value of prognostic research in adult patients with severe TBI, test model feasibility and develop new prediction models for TBI population in LMICs, specifically in terms of predicting mortality and functional outcome.

In the narrative review in Chapter 2, we found 20 studies that met the stated search criteria, 15 of these papers aimed to develop new prognostic models; however, only five of the newly developed models were validated. The results of our review also point out that the majority of current models (85%) were developed from participants in high-income countries (HICs). Additionally, through use of the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist[62] as a tool to examine the quality of reporting prognostic research, we found many studies did not meet quality reporting criteria. Specifically, published articles fell short of describing the flow of patients through the study, explaining the type of biological materials used and their handling methods as well as presenting estimated effects of key variables with confidence intervals. These findings reveal the gaps in knowledge and also provide recommendations to refine future TBI prognostic research, which was presented in Chapter 2.

Chapter 3 discussed the need to develop generalizability of the gold standard models and determine their ability to reliably predict outcomes in new populations, especially in LMICs. In this chapter, we examined the applicability and external validity of the International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT)[8] and Corticosteroid Randomization after Significant Head Injury (CRASH) models for outcome prediction following TBI[8] using a South-American cohort. Although the overall performance of all IMPACT and CRASH models was adequate when applied in this dataset, the IMPACT lab model is preferable as it presents a higher discriminative capacity than the CRASH models.

Our findings are contradictory with other studies that stated the CRASH models were developed from a substantial number of patients from LMICs and included additional information from major extracranial injury (MEI).[15 25 76] As such the models should perform better than the IMPACT models when the population under the study includes patients from LMICs. Since the majority of patient information in the South-American dataset was retrieved from a clinical trial that used relatively strict enrolment criteria to decrease the inherent heterogeneity of TBI; there was a higher number of cases with severe injury and less incidence of major extracranial injury (MEI), hypoxia, and hypotension than the participants from the IMPACT and CRASH studies. For future external validation research in other samples, it would be beneficial to use broad enrolment criteria with adjustment for the heterogeneity in the analysis phase by covariate adjustment. This approach may help to ensure that the poor performance on external validation is not affected by the differences in patient characteristics.[19]

Thailand is a MIC that has a high mortality rate of TBI[85] and notes to have limited resources for TBI management like other LMICs. It may be inappropriate to extrapolate models from HICs for use in this setting. Thus, the goal of Chapter 4 was to develop a new prognostic model for severe TBI based on patient admission characteristics and compare this model to the performance of the set of variables in the IMPACT and CRASH core models. We found patient pre-injury comorbidity, anisocoria, glucose level, and motor response post-resuscitation were independent predictors of in-hospital mortality. For functional outcome measured by GOS, respiratory rate at hospital admission, hematocrit, and Glasgow Coma Scale (GCS) score post-resuscitation were independent predictors. Overall, the Thai model for predicting in-hospital mortality had the best performance. Unlike other studies validated IMPACT and CRASH models, we did not include the prognostic information from the computed tomography (CT) scan. This was because the study hospital has a limited number of radiologists, and Marshall's CT classification is not usually implemented; thus, we decided not to exploit this variable in the analyses. Thus, the set of the variables in IMPACT CT and Lab models, as well as the CRASH CT model, were not compared to the new Thai models in our study. Although the shortcomings encountered from a retrospective cohort design, the Thailand study reveals the prognostic value of readily available, commonly collected variables like patient vital signs, hematocrit, and glucose level. The vital signs and laboratory test are routinely measured during TBI hospital care, and the values are objective. The benefit of using these variables is that they are potentially modifiable. Therefore, clinicians can use this information to guide clinical decision in modifying their plan of care.

Limitations

Although this dissertation contributes further to the evidence based on the performance of prognostic models for severe TBI patients, there are some limitations in each chapter that should be noted.

Firstly in Chapter 2, PubMed was the only database used in our search. The specific combination of the terms "prognostic model" and "traumatic brain injury" was implemented, and the search was limited to studies published during 2006 - 2019. Therefore, we might have missed some reports that were posted on other databases or used different keywords as their search terms. We also acknowledge that other systematic reviews for prognostic models published recently restricted the search to 1970[66] and 1990[12] onwards. However, because of changes in management and diagnostic technology in recent years, we doubt that prognostic models published previous to 1970 could be useful for the current medical care of TBI patients.

Secondly, the South American dataset using in Chapter 3 was not designed for predicting the outcome after TBI based on patients admission characteristics. Therefore, some important admission characteristics were missing in more than 10% of subjects; these variables included the Glasgow Coma Scale (GCS) and motor response. Also, the percentage of subjects who have variables of interest in the South American dataset is very different than the percentage of cases in the IMPACT and CRASH data set. The participants in our data were clinically more severely injured when considered their motor response, the presence of SAH and EDH on CT scans; while the incidence of MEI, hypoxia, and hypotension were lower in our data set. These limitations may have influenced the results.

Finally, The Thai models in Chapter 4 were developed on relatively small patient series (N =316), and the study population originated from a single center. Although we originally planned to validate the Thai models on the external population using the South American dataset, we found it was the most challenging task. We were unable to complete the planned analysis as the South American dataset does not contain information regarding respiratory rate and patient pre-injury comorbidity, which were two important prognostic factors in the Thai models. Moreover, the Thai models were developed from the retrospective dataset, and this might produce biases regarding patient characteristics, data collection, and analysis. Thus, there is a need for development and validation of the Thai models based on large patient population from multiple centers to enhance model generalizability.

When considering the dissertation as a whole, we encountered several limitations from different processes as follow:

Pre-data collection

There were several research studies conducted at the same time in the study hospital. It delayed approval from the Ethical committee at the Thailand hospital. Also, the study proposal and all the data collection forms were required to translate in Thai. This process had push back the study timeline for almost three months. Moreover, one of the study hospital regulation for a researcher when conducting medical record review is that the researcher must work at the hospital registry department during there office hours (8.30 am – 4.30 pm). It was a challenge finding qualified research assistants (RA) who were available during those hours, as all the RAs were the registered nurses who work in the neurosurgical critical care unit where they also had the day-shifts (8.30 am – 4.30 pm).

Data collection

Once the medical records were reviewed, we found that the Glasgow outcome scale (GOS) was not a standard outcome measure assessed by the neurosurgeons at the study hospital. Fortunately, there was a nurse manager at the neurological outpatient department who document every patient’s GOS during their follow-up. The information from GOS was used for hospital administrative purpose only, and the person recording this data was not systematically trained to assess GOS. There were also some issues related to the patient data record. We loss many eligible participants as they were transferred to other hospitals, and those hospitals did not share patient records. Many available records were frequently inconsistent and incomplete. Marshall’s CT classification was not implemented at this hospital.

Data analysis

We obtained the South American dataset for the IMPACT and CRASH models validation. The dataset was complex and required a sophisticated statistical software as the Statistical Package for the Social Sciences (SPSS) software from IBM (version 25.2; Chicago, Illinois) for data analyses. However, the SPSS does not have a direct function to calculate C-statistics from the bootstrap samples. Thus, some of our analyses were performed on the other software as well (Statistical Analysis Software: SAS®).

Implications for Research

The main research applications of prognostic models for outcome in TBI are to 1) classify the patient population using their predictive risk and 2) determine eligibility and adjust for patient baseline characteristics. Prognostic risk estimation on hospital admission allows populations to be classified according to their prognostic risk distribution. This mean of characterization provides integrated insight into variation in the case-mix of different studies,[65] and would help to identify the subgroup of patients likely to benefit from a given targeted intervention under investigation.[20] A prognostic model can also strengthen the design and analysis of clinical trials through the enrolment and analysis phase.[15] For example, in this dissertation which the Thai dataset was conducted using relatively strict enrolment criteria on admission to ensure we recruited TBI patients with less heterogeneity. Therefore, it requires us to retrieve more patient data and required more resources to complete data collection to satisfy expected statistical power. Lingsma et al. suggest that it is statistically more efficient to combine enrolment criteria in a prognostic model.[65] Also in the analysis phase, the prognostic model can adjust for baseline characteristics. This approach increases statistical power and allows the requires sample size to be reduced by more than 25%.[8]

There are some future research questions needed to be answered. One of the most important issues would be whether different patient characteristics in validation dataset can affect model performance. Our study found blood glucose level and hematocrit at ED admission were associated with outcome following TBI. However, the amount of red blood cell transfusion (RBCT) was also related to increase ICU length of stay and mortality.[97] [99] Also, no solid evidence exists that tight glycemic control improves outcome in TBI patients. On the contrary, it might lead to hypoglycemic episode with deleterious effect on the injured brain.[100] Future studies are needed to explore an optimal and safe hemoglobin or hematocrit level and glycemic range and rate of change to facilitate critical care of anemia and blood glucose control. Lastly, This study revealed that an increase in respiratory rate was a protective risk factor against unfavorable outcome after TBI. The Guidelines for the Management of Severe TBI suggests that unless hyperventilation is unavoidable during the first 24 hours after injury; patient's oxygen delivery should be monitored using advanced technologies such as brain tissue O_2 partial pressure ($BtpO_2$).[101] This recommendation is not applicable to settings where high-technology monitoring is limited. Further study should be conducted to determine the relationship between respiratory rate and functional outcome after TBI.

Implications for Nursing Practice

Nurses have a multifaceted role in the care of patients with TBI. As an essential member of the interdisciplinary team, they hold numerous responsibilities to assist with the patient's treatment and recovery. These roles include assessing the patient, coordinating and communicating care, conducting technical and physical care, integrating prescribed therapies, providing emotional support to the patient and their family, advocating for the patient, involving the patient and family in care, and educating the patient and family.[35] One of the most critical responsibilities for nurses in caring for patients with TBI is modifying their plan of care regarding the changes in patient's condition. Usually, such modification relies on the ability to make a clinical decision based on patient characteristics, for example, the Glasgow Coma Scale (GCS) score, age of the patient, the presence of extra-cranial injuries and other comorbidities.[9]

Having a more accurate understanding regarding the prognosis of a patient can help nurses in proper planning and provision of care to these patients as well as their families. On the contrary, incorrect estimation of prognosis can lead to mistakes, where patients who are thought to have a poor prognosis may not be provided optimal care, resulting in a poor outcome.[9 35 36] Also, concern about the outcome is often foremost in the mind of the relative of patients with TBI.[36] In acute care settings, nurses may find it challenging to respond accurately when the families or caregivers of the patients ask about their expectations of recovery. Once the questions are raised, realistic counseling is preferable to over pessimism or the raising of false hopes; and nurses should be well informed concerning what information regarding prognosis should be shared with the families.

Although in our dissertation, we found that the IMPACT models may be useful for quantifying the severity of brain injury for research studies, the models were inadequate to apply in individual patients as a tool to provide practical information to relatives on expectations of outcome or as an indicator to guide treatment resource allocation. However, with the findings from the Thai model validation, we found new independent predictors (vital signs, laboratory test, and comorbidity) that were strongly associated with the patient outcomes. The variables were usually assessed and collected for all patients by clinician or nurses. This highlights the importance of standardized patient monitoring and documentation. The value of patient clinical information in the evaluation of patients with TBI in the acute phase could enhance the quality of care and clinical research. Finally, the knowledge from the prognostic study could be an objective way to transfer knowledge of patient assessment among nurses with different expertise as well.

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