PREDICTING OUTCOME AFTER SEVERE TRAUMATIC BRAIN INJURY

By

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To my mom

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I thank the chair and members of my committee for their mentorship. I thank my family and friends for their encouragement throughout this process.

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Outcomes for patients who survive a severe TBI vary considerably. Researchers strive to predict not only mortality but also long term outcome. A recent model has proven to predict crude outcome after severe TBI. The present study sought to replicate and extend these findings to provide more detailed characterization of outcome at 6-months post-injury.

Participants consisted of 546 adults ages 18-89 with severe TBI. Acute physiological data was gathered for use in the extended IMPACT model and included: patient's age, pupil response, GCS motor score, CT characteristics, as well as events of hypoxia and hypotension. Outcome measures obtained at 6-month post injury included mortality, favorable/unfavorable outcome on the Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), and Digit Span.

This study replicated the IMPACT study findings and showed that the model is sensitive and specific for predicting mortality and favorable outcome in this sample. The model shows promise for using acute physiological data to predict detailed long-term outcome. The model showed limited utility when predicting cognitive working memory ability 6 months after injury.

The current model shows promise for creating more precise classifications of injury severity to help reduce the heterogeneity among severe TBI patients for research purposes and clinical trials. From a clinical standpoint, more precision in severe TBI classification could provide a more accurate clinical picture than is currently available which would enable quicker responses and better exchange of information among physicians. The IMPACT model could provide a powerful tool to communicate information among clinicians and to patient's families.

CHAPTER 1
BACKGROUND

Introduction

Patients who suffer severe traumatic brain injuries (TBI) are frequently admitted to the hospital in very critical condition. These early stages are pivotal for patient survival, and physicians must often make quick decisions regarding the use of certain therapeutic interventions. For this reason, prognostic models have been developed to use data that can be obtained promptly upon admission to detect a patient's declining medical status and determine whether more aggressive interventions should be initiated. Researchers have recently used data a from large multisite sample from the International Mission for Prognosis and Analysis of Clinical Trials project to create a prognostic model (IMPACT model) that can effectively predict mortality at six months after a TBI (Steyerberg et al., 2008). However, once patients have been stabilized, the concerns of the practitioners and families change from keeping a patient alive to maximizing their recovery. As patients continue to recover, plans are made for their discharge from the hospital and decisions are made regarding rehabilitation services and supervision needs (De Guise et al., 2006). This task is becoming increasingly more difficult as the length of stay in the hospital has been continually decreasing over time for TBI patients (Ashley & Ashley, 2004). Discharge planners now have less time and less information to make suitable plans for rehabilitation or home environment. More sensitive prognostic information is important in the counseling of patients and loved ones at this important time regarding outcome beyond general Favorable or Unfavorable including issues of independent living, employment, and leisure activities (Perel et al., 2006).

A prognostic model that could predict more detailed outcome would be a valuable asset to assist in the process of discharge planning. This could give families a better idea of what to expect long term in reference to a wider range of global functioning and a more detailed picture of cognitive functioning. The current study proposal builds upon the previously validated prognostic model of TBI outcome based on the extensive IMPACT study. The IMPACT model as it has been produced only predicts to gross outcome. The current proposal seeks to determine whether more specific levels of long term functioning including cognitive abilities can be predicted. The following sections will briefly review previous efforts to identify acute clinical variables that contribute to the predictive ability of prognostic models in TBI. Research on each of the individual predictors used in the IMPACT model will be presented. A great deal of research has been conducted regarding the predictor variables; however, methods of measuring outcome have been less well developed. Therefore, research regarding the issues of feasibility, ecological validity, and psychometric properties of different methods of outcome measurement will be discussed.

Existing Prognostic Models

Existing prognostic models have revealed various combinations of acute clinical variables associated with general outcome after TBI. Several early outcome studies found that the admission Glasgow Coma Scale (GCS) score, when combined with age and pupil reactions were accurate in predicting mortality and morbidity (Jennett et al., 1976; Choi et al., 1983; Narayan et al., 1981). Studies then began to build on these predictors and examined the contributions of other variables such as CT data (Choi et al., 1983), period of post traumatic amnesia (Bishara et al., 1992; Ellenberg et al., 1996), intracranial pressure (Narayan et al., 1981) and cerebral perfusion pressure

(Changaris et al., 1987). These outcome studies, like others carried out in acute care settings, have focused on mortality and morbidity (Elf et al., 2002, Jeremitsky et al., 2003). Over the years, many prognostic models have been developed, but few have been widely used due to small sample sizes and poor methodology (Young and Andrews, 2008).

The creators of the IMPACT model (Steyerberg et al., 2008) argued that many attempts at developing prognostic models for TBI have fallen short due to small sample sizes, lack of external validation, and impractical presentation of the model for clinicians. To remedy these problems, they developed a prognostic model for TBI using a meta-analysis of 11 studies in the very large multi-site IMPACT database using a sample of 8,509 patients (Maas et al. 2007). These studies included three observational studies and eight randomized control trials conducted between 1984 and 1997. They included patients aged 14 years and older with moderate to severe TBI as defined by a GCS less than or equal to 12. In order to externally validate their model, they used another large database of 6,681 TBI patients from the Medical Research Council Corticosteroid Randomization after Significant Head Injury trial (MRC CRASH trial collaborators, 2008) who participated between 1999 and 2004. This was a large international trial of the administration of methylprednisolone after head injury. To address the potential confound of the administration of the drug, secondary analyses were performed with only placebo patients. Twenty-six potential predictors including demographic, injury severity, CT, biochemical, and secondary insult variables were tested. They found that age, GCS motor score, and pupil response were the most predictive of general outcome at the six month time point (Steyerberg et al., 2008). These three predictors constituted

their Core model which is consistent with many previous models for TBI (Jennett et al 1976; Perel et al 2006). An Extended model was also developed that included the three predictors from the core model, but added information on secondary insults (e.g., hypoxia, hypotension) as well as CT characteristics. This Extended model provided additional prognostic information to the Core model (see Table 1-1). With this extensive database, the IMPACT model for TBI addressed many of the limitations of previous models to predict mortality at six months post injury.

Table 1-1. Impact models

Core Model	Extended model
Age	
GCS motor score	Core Model
Pupil response	
	CT characteristics
	Marshall Classification
	Traumatic Subarachnoid hemorrhage (tSAH)
	Epidural hematoma (EH)
	Secondary Injury
	Hypotension
	Hypoxia

Predictors Used in Prognostic Models

Each of the individual predictors used in the IMPACT prediction formula has been extensively examined for its utility in the prediction of outcome after severe TBI.

Glasgow Coma Scale (GCS)

The GCS is comprised of three scales including eye opening, verbal response and motor response. These three values can be considered separately, but most frequently they are summed to create a single score. The lowest possible GCS is 3 (deep coma or death), and the highest is 15 (fully conscious; Teasdale and Jennett, 1974). Since its introduction in 1974, the GCS has become one of the most widely used

tools for assessing brain injury severity because it can be quickly performed, it is repeatable, and it serves as an effective means to communicate brain injury information with other members of the treatment team in a standardized way (Jennett 2002; McNett 2007). Emergency personnel frequently use the GCS score with head injured patients to make clinical decisions in the very acute phases (i.e. appropriate facilities to take a patient, appropriate treatment protocols; Jennett, 2002). The developers of the scale argue that the use of the GCS in frequent monitoring of brain injured patients has led to better outcomes in many cases because it enables clinicians to detect deterioration earlier so they can intervene more quickly (Jennett 2002). These features of the GCS have lead researchers to study the GCS extensively for its validity in predicting functional outcome and mortality (McNett, 2007). Studies have shown that the GCS in combination with other variables can be useful in predicting outcome after TBI when broad outcome categories are used.

The GCS has served its intended purpose of providing a quick and easy method for assessing TBI severity. Nevertheless, there are some challenges in using GCS as a predictor. Researchers have often used different GCS assessment time points for their prognostic models. GCS scores have been used from admission to the first hospital, some admission to the study hospital, or a combination of these time points (Marmarou et al., 1999; Murray et al., 1999). In fact, patients can vary significantly across early time points due to a variety of confounding variables (McNett, 2007). When obtained within the first few hours after injury, GCS scores can be influenced by the presence of drugs or alcohol. Later scores can be complicated by sedation, intubation or tracheostomy. The developers of this scale assert that the most valid time to measure GCS is after

resuscitation (Jennett, 2002), and of course prognostic variables are most valuable when they can be accurately obtained early in the intervention process.

One drawback the IMPACT is that the studies drawn from to create the database ranged from within 4 hours of injury to 3 days post injury in the time point the GCS was administered (Marmarou et al., 2007). They attempted to obtain time points as close as possible to post resuscitation GCS, but at the same time efforts were made to maximize the number of patients in the database (Marmarou et al., 2007). Prognostic models are most effective when the predictors are gathered in consistent ways at consistent time points.

Age

A patient's age is another variable commonly used in the prediction of outcome after severe TBI. Increasing age has been associated with both a higher likelihood of mortality and a poorer general outcome from severe TBI (Howard et al,. 1989, Mosenthal et al., 2002). Howard and colleagues (1989) noted that despite comparable GCS scores, outcome was worse in the elderly, suggesting that GCS scores can underestimate the severity of brain injury in the elderly. The reasons for these worse outcomes remain unclear; however, several studies have suggested differences in the mechanism of injury, therapeutic interventions, complication rate, and premorbid disease (Hukkelhoven et al., 2003). Hukkelhoven and colleagues (2003) hypothesized that the brain has a lower capacity to heal as it ages resulting in a decreasing number of functioning neurons. Additionally, older individuals may experience a cumulative effect of minor insults to the brain as age increases (Hukkelhoven, 2003). These mechanisms suggest that the elderly may experience more significant loss of cognitive functioning after TBI. Age is therefore an important variable to include in a prognostic model as it is

likely to contribute significantly to cognitive outcome and it has demonstrated utility in addition to the GCS score.

Pupil Response

Another acute clinical variable that has been commonly used in prognostic models is pupil response upon admission. Pupil response is fundamental to neurological assessment because poor reactivity or dilation of the pupils may be related to compression of the oculomotor nerve and indicate brainstem dysfunction (Marmarou et al., 2007). Variation in pupil response may be indicative of different underlying causes such as uncal herniation or reduced blood flow to the brain stem (Ropper et al., 1991; Ritter et al., 1999). Damage to the brain stem can quickly become lethal as it can result in problems with autoregulation or changes in blood pressure (Ritter et al., 1999). Several studies have shown a strong relationship between absence of pupil response and poor outcome after TBI (Andrews et al., 2002; Marmarou et al., 2007). Additionally, the combination of fixed dilated pupils with low GCS scores has been shown to be a powerful predictor of mortality (Jain et al., 2008). Thus, pupil response has been shown to be a robust prognostic indicator and is widely accepted as an important clinical variable to include in outcome prediction models for severe TBI.

Structural Neuroimaging

As highlighted in the IMPACT model, there are additional prognostic variables that can strengthen the Core model including information regarding structural neuroimaging. Computed tomography (CT) of the brain has commonly been used as an additional acute indicator of brain injury characteristics. CT imaging is used in the acute stage of TBI to detect gross structural brain abnormalities and identify the need for medical or surgical intervention, because it can be done quickly and inexpensively

(Haydel et al., 2000). Despite its lower resolution, CT is preferable to magnetic resonance (MR) imaging for acute TBI patients, because unlike MR, it can even be done with common metal-based life-support equipment in place (Bigler 2005). Head CT has proved to be an excellent clinical tool in detecting some lesions, hemorrhages, skull fractures, and swelling (Bigler 2005). Marshall et al. (1992) created a CT rating scale that provides a basis for evaluating the severity of injury during the acute stage. This classification system identifies 6 categories describing the extent and nature of the brain injury based on CT scan abnormalities. The Marshall CT classification system has become widely accepted for descriptive purposes and has been shown to be a strong predictor of general outcome in TBI (Hukkelhoven et al., 2005; Lobato et al., 1983; Servadei et al., 2000).

One drawback to this system is that although it distinguishes between the presence and absence of brain hemorrhage requiring surgical intervention from those that do not, it does not describe critical information about the location of bleeding. More specifically it is understood that bleeding occurring above the dura has different prognostic implications compared to bleeding below the dura (Maas et al., 2005). Maas and colleagues (2005) found that the inclusion of additional CT characteristics in a model can add prognostic value to the Marshall classification alone. For example, the presence of traumatic subarachnoid hemorrhages (tSAH) and epidural hematomas (EH) has been shown to be a strong predictor of outcome and mortality in TBI and have been recommended for inclusion in prognostic models of severe TBI (Maas et al., 2005; Servadei et al., 2002). Despite the utility of CT in identifying gross structural pathology in the acute stage, these findings have not been shown to relate well to cognitive

outcome at the time of discharge from rehabilitation, which has made the accurate prediction of outcome from acute CT findings alone difficult (Dikmen et al. 2001; Temkin et al. 2003). While CT findings cannot alone predict cognitive outcome after severe TBI, they do make a significant contribution to a prognostic model.

Secondary injury

Damage to the brain sustained from a severe TBI is classified as primary if it is related to the initial trauma and secondary if it is related to any events that occur afterward. Following the primary injuries, the brain becomes more vulnerable to secondary damage (McHugh et al., 2007). Of the types of secondary injury that have been studies thus far, hypoxia and hypotension have proven most valuable predictors of outcome in prognostic models of severe TBI (Andrews et al., 2002). Associations have been found for both of these two markers of secondary insults and adverse outcome after TBI (Manley et al., 2001; Walia and Sutcliffe, 2002; Chesnut, 1993). Both of these injury markers are relatively common on admission and their combined effects are substantially greater than the sum of the individual effects (McHugh et al., 2007). Therefore, these indicators of secondary injury will likely contribute to the prognostic value to a model of cognitive outcome after severe TBI.

Measurement of Outcome after Traumatic Brain Injury

Extensive research has been conducted on ways to measure and combine various acute physiological variables in severe TBI to create prognostic models with great statistical power. Research on outcome measurement, on the other hand, has lagged behind. The ideal measure of TBI outcome would be easily administered, ecologically valid, reliable, and sensitive to a wide range of outcomes. Unfortunately,

such a measure does not yet exist. Each of the existing measures that are commonly used in TBI outcome research comes with its own pros and cons.

Many studies simply ask whether patients returned to work after their injury (Wehman et al., 2005). Although this outcome is certainly ecologically valid and can be easily assessed, it is wrought with confounds that may call its validity into question such as a patient's premorbid employment or the role of other physical injuries unrelated to the TBI. Scales have been created that classify TBI outcome into global categories of functioning such as the Glasgow Outcome Scale (Jennett and Teasdale, 1975). These measures tend to be easy to administer but often suffer from poor sensitivity and inter-rater reliability (McCauley et al., 2001).

Efforts have been made to create outcome measures that remove these flaws; however, there is often a trade-off such that when a test becomes more sensitive and reliable, it becomes more difficult to administer. Neuropsychological tests provide a means of measuring cognitive functioning after TBI with excellent psychometric properties and high sensitivity to subtle differences. However, these tests often require a lot of time to administer and some must be administered and interpreted by trained professionals. The following sections outline some specific examples of measures used in TBI outcome research and their strengths and weaknesses.

Global Functional Outcome

As described earlier, most of the prognostic models developed thus far have predicted recovery in a general way using crude variables such as mortality or global outcome as measured by the Glasgow Outcome Scale (GOS, Jennett and Bond 1975). The GOS has long been a widely used measure of both short and long term recovery from TBI that provides a quick assessment of functional outcomes with clinical

relevance (Satz, 1998). This scale categorizes outcome into 5 general categories: (1) Death; (2) Persistent Vegetative State; (3) Severe Disability; (4) Moderate Disability; and (5) Good Recovery (Jennett and Bond 1975). The scale is not intended to provide detailed information about the specific difficulties faced by individual patients, but to give a general index of overall outcome (Marshall, 1992). It has been recommended for use in clinical trials as it was intended to compare patients in a simple easily interpreted way (Clifton et al., 1993). GOS has traditionally been obtained through a short unstructured interview which has led to poor inter rater reliability (Anderson et al., 1993). Different versions of this scale have been developed to address some of its shortcomings by including a structured interview to increase reliability and expanding the number of categories to increase sensitivity (Wilson et al., 1998).

For the purpose of prognostic model development, the GOS is often collapsed further into fewer categories. In TBI outcome prediction studies the scale has been traditionally dichotomized into Unfavorable outcome (Death, Vegetative State or Severe Disability) and Favorable outcome (Moderate Disability or Good Recovery; McHugh et al., 2007). These levels of outcome are generally adequate for studies in acute care settings where doctors' early focus is primarily on mortality and morbidity (Ashley & Ashley, 2004). However, once patients have stabilized, more sensitive measures of outcome become necessary to assess the full range of outcome possible after TBI (Clifton, 1993).

Although the GOS is widely accepted as a standard way of classifying recovery after TBI some have argued that this scale may sacrifice detail for simplicity in its broad classifications of outcome (Clifton, 1993). This scale has been shown to be insensitive

to clinically significant changes in patient states (Hall, 1985; Struchen et al., 2001). Because of this insensitivity it has proven difficult to document patient recovery over time using this scale (Clifton, 1993). Moreover, many patients with good GOS scores have been shown to have significant functional deficits as measured by more specific neurobehavioral tests (Satz, 1998). In fact, the GOS has been criticized for emphasizing the physical symptoms and while disregarding mental changes that are often more important in determining disability after TBI (Anderson et al., 1993). The developers of this scale contend that it serves its intended purpose of facilitating inter-center communication and comparison regarding TBI outcome (Jennett and Bond 1975). However, Wilson and colleagues (1998) noted that other more detailed measures of impairment and disability should supplement the GOS when used as a primary outcome measure.

The Disability Rating Scale (DRS) is another accepted measure of global outcome after TBI that may be more sensitive to changes in functioning (Rappaport et al., 1982). The DRS assesses more detailed levels of feeding, grooming, and toileting abilities and includes related issues such as dependence on others and psychosocial adaptability (Rappaport et al., 1982). The DRS can thereby characterize patients on a full range of outcomes from coma to reentry into the community. The DRS has demonstrated excellent inter-rater reliability, and test-retest reliability (Novack, 1991; Gouvier, 1987). Furthermore, the predictive validity of the DRS has been demonstrated through correlations with length of hospital stay, disposition at discharge, and DRS one year later (Eliason and Topp, 1984; Rappaport et al., 1982). Additionally, the DRS has been shown to have ecological validity as it was able to predict return to competitive

employment (Cope et al., 1991). Overall, the DRS has proven to be a sensitive, functional, reliable, and ecologically valid means of monitoring patients with traumatic head injury during the course of their recovery.

Cognitive Outcome

The GOS and DRS provide adequate estimates of general outcome after TBI that have demonstrated ecological validity. However, other types of outcome measurement would be helpful in discharge planning and determining on whom to target limited rehabilitation resources (Clifton, 1993). Some researchers have argued that due to the complexity of recovery from TBI, multiple dimensions of outcome should be explored. Novack et al. (2001) proposed a theoretical framework for the nature of outcome after TBI that includes cognitive, emotional, and functional status. In this study the relationships among the multiple components of outcome were evaluated, and it was found that injury characteristics could not only be used to predict functional skills but also cognitive status. Additionally, cognitive status was found to have a particularly strong relationship with measures designed to capture overall functional outcome, suggesting that cognitive abilities play a significant role in recovery (Novack, 2001). Further, Rassovsky and colleagues (2006) found that TBI severity exerted an indirect rather than direct impact on functional outcome. This study explored potential mediators of the relationship between TBI severity and overall outcome, and they determined that cognitive functioning was the most significant mediator (Rassovsky 2006). This research supports the role of neuropsychological testing in TBI outcome research. Such testing can contribute a reliable forecast of functional ability to both the family and rehabilitation team.

Specifically, neuropsychological measures have provided a valuable characterization of the nature of common cognitive impairments after TBI. Most commonly these patients have demonstrated deficits in attention, reduced capacity for new learning, and slowed information processing (Dikmen, 1993; Millis, 2001). Additionally, deficits in motor skills, executive functions, and overall intellectual skills have been identified (Dikmen, 1993). The extent of these impairments has been found to be related to the severity of the TBI (Millis, 2001). However, these studies have commonly relied on crude measures of injury severity. Additionally, these studies revealed great variability of performance within severity levels. Dikmen et al. (1993) argued that this heterogeneity may be taken as a sign of failure to appropriately classify severity. Studies that have specifically examined cognitive functioning have not utilized the full range of injury characteristics. More detailed assessment of injury characteristics used in prediction may help to understand the variability seen in neuropsychological outcome among patients with severe TBI.

Neuropsychological batteries can provide an in depth look at the nature of cognitive deficits, but they require a significant investment of time and energy from both the patients and examiners. Because of these heavy demands on patients' time and effort, following them long term becomes more difficult even when compensation is provided and extensive efforts are made to make participation more convenient for patients. Longitudinal studies that use long-term cognitive outcome measures have notoriously high attrition rates. Studies have reported having almost 50% attrition rate for six month cognitive outcome, which is considerably higher than is most often achieved with non-cognitive outcome measures (Struchen et al., 2001). Additionally, a

significant portion of survivors of TBI remain to disabled to complete a full traditional battery of neuropsychological tests (Clifton 1993). Thus, there are considerable obstacles that of prevent the use neuropsychological tests as primary outcome measures in TBI recovery research.

Researchers have sought to remedy this problem by reducing the size of the neuropsychological battery and selecting tests that give the most bang for your buck (Clifton et al., 1993; Satz et al., 1998). The optimal test of cognitive functioning would be brief and easily administered so that a non-neuropsychologist could give it at bedside or even over the phone. Ideally, this test would also minimize physical confounds related to motor or visual impairments. Additionally, the test would be sensitive to the full range of outcomes that can occur after TBI and not be subject to floor effects. With hundreds of cognitive assessment tools to choose from there are some tests that come closer to reaching these criteria than others. As described above the areas of common deficits after TBI include information processing speed, attention, memory, and executive functioning. Tests of processing speed typically have a heavy motor component that may introduce a confounding factor for TBI patients with impaired motor functioning in limbs. Furthermore, many tests of executive functioning are difficult to perform and are subject to floor effects in a severe TBI population.

A simple test of attention and working memory such as Digit Span may be the best candidate to fit the above criteria as it is easy to administer, sufficiently sensitive, and has no motor or visual component. Digit Span tests consist of both forward and backward conditions, each of which involves slightly different mental activities. Forward span tasks are typically considered measures of attention and immediate recall (Lezak

et al., 2004). Forward digit repetition is often impaired in the first months following head trauma, but over time performance returns to normal (Lezak, 1979). Backward span tasks, with the added requirement of mentally reversing the numbers, are regarded as measures of working memory (Lezak et al., 2004) The backward condition has been found to be very vulnerable to diffuse damage and has been shown to be impaired following TBI (Fork et al., 2005). Both forward and backward digit spans measure the adverse effects of brain injury on cognitive abilities of attention and working memory. Given its ability to measure these deficits, previous research has classified the Digit Span task among psychological assessment tools with demonstrated robustness in the prediction of everyday functioning (Tupper and Cicerone, 1990). However, it has been argued that level of education should be taken into account when using this outcome, as it has been demonstrated that education is a strong predictor of both forward and backward digit span (Ostrosky-Solı´s and Lozano, 2006). Nevertheless, the addition of a cognitive measure of outcome such as Digit Span could provide a powerful supplement to the previously described global measures that are ecologically valid.

CHAPTER 2
OVERVIEW AND STATEMENT OF THE PROBLEM

Introduction

TBI research has long sought to create a means to accurately predict long term outcome. The review of the literature presented above suggests that the IMPACT model has proven to be useful in predicting mortality or crude general outcome after severe TBI (Steyerberg et al., 2008). However, this model has not demonstrated the ability to predict more detailed outcomes. Part of the challenge of this process is the choice of outcome measures. The state of measurement development leaves us with a tradeoff between ecological validity and sound psychometric properties. The overall goal of this study is to replicate the main findings of the IMPACT model and to extend these findings by using measures that will provide more detailed characterization of outcomes.

Using the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) Study Model to Predict Outcome

The creators of the IMPACT model have developed a scoring system that allows clinicians to calculate the probability of prognosis for a particular patient. To create this scoring system, the predictor variable from the Core and Extended IMPACT models were used in proportional odds logistic regression analysis with 6 month GOS as the outcome measure. The regression coefficients from these analyses were rounded and scaled to create a score chart for each of the models (see Figure 2-1).

Figure 2-1. IMPACT model score chart for 6-month outcome after TBI

Characteristics	Value	Score (*b*)
Age (years)	≤ 30	0
	30 - 39	1
	40 - 49	2
	50 - 59	3
	60 - 69	4
	70 +	5
GCS Motor Score	None/extension	6
	Abnormal flexion	4
	Normal flexion	2
	Localizes/obeys	0
Pupil Response	Both pupils reacted	0
	One pupil reacted	2
	No pupil reacted	4
	Total Score Core Model	_____
Hypoxia	Yes or suspected	1
	No	0
Hypotension	Yes or suspected	2
	No	0
CT classification	I	-2
	II	0
	III/IV	2
	V/VI	2
tSAH	Yes	2
	No	0
EH	Yes	-2
	No	0
	Extended Model Subtotal	_____
	Total Score Extended Model	_____

The IMPACT model score chart is used to calculate the probability of an Unfavorable outcome at six months post injury and is derived from a logistic regression equation in the form of: $P(Y) = (1/(1+e^{-LP})$. In this case $P(Y)$ is the probability of an Unfavorable outcome at six months post injury and *e* is the base of natural logarithms. LP refers to the linear predictor in a logistic regression model in the form of: $LP = b_0 + b_1X_1 + b_2 X_2 + ... + b_n$. The constant ($b_0$) or intercept of the line is based on previously published calculation of proportion of Unfavorable outcomes in severe TBI, and (X_n) represent the series of predictor variables with coefficients (or weights) attached to each predictor (b_n). This formula shows that the predictors (X_1-X_n) are on a scale related to

the probability of Unfavorable outcome with relative weights (b_1-b_2) derived from the regression coefficients rather than odds ratios (Moon et al., 2002). This means that for a patient with a particular profile, the regression coefficients b_n are multiplied by each of the patient's corresponding X_n values which can then simply be added together creating the sum scores. The resulting equations become:

LP_{core} = -1.62 + 0.299 x Sum score of Core model

$LP_{extended}$ = -2.10 + 0.276 x (Sum score of Core model + subscore CT)

The resulting value can then be logistically transformed according to equation one to calculate that patient's probability of Unfavorable outcome P(*Y*). The regression coefficients have been scaled and rounded to the nearest integer so that scores for each predictor can be easily obtained and used for both the Core and Extended models. In this way relative risks of the individual predictor variables can be combined into a single prognostic variable that is indicative of the risk of an Unfavorable outcome at six months post injury. By entering a patient's raw prediction data into this IMPACT model score chart and then using the resulting Total scores in these equations, one can establish the probability of Unfavorable outcome at six months.

The discriminatory ability of the core model had an area under the receiver operating characteristic curve (AUC) between .66 and .84 at cross validation with the CRASH database. The extended model improved the AUC by .05 suggesting these models were both highly effective in predicting general outcome categories. This finding could suggest that there is little added value to including the additional information

contained in the Extended model. However, this has not been established for other measures of outcome.

Unfortunately, the studies that were merged to form the IMPACT database lacked uniformity in data collection for some of the measures. The GCS scores used in the studies were administered at time points that ranged from within 4 to 72 hours post injury, but when possible the post-stabilization GCS was used (Marmarou et al., 2007). Pupil response was likewise measured at various times which coincided with administration of the GCS. The same time points were used for both. Information regarding pre-enrollment hypotension and hypoxia was gathered for 9 of the studies. Hypotension was defined as systolic blood pressure < 90 mmHg and hypoxia was defined as partial pressure of oxygen (pO_2) < 60 mmHg. Head CT scans obtained on admission that provided Marshall classifications as well as information regarding tSAH and EDH were obtained in seven of the studies. Although some discrepancies exist from merging data from multiple studies, the data in the IMPACT database underwent rigorous quality control measures and is reported to be at a very high standard (Marmarou et al., 2007). The IMPACT model from Steyerberg et al., (2008) was selected for this study because it was based on a large sample, externally validated, and had sound methodology.

Aim 1

The first aim of the current study was to replicate the Core and Extended IMPACT models using the same global outcome classifications more specifically mortality and dichotomous GOS scores classified as Favorable (Moderate Disability or Good Recovery) or Unfavorable (Death, Vegetative State or Severe Disability). It was

hypothesized that the results would be similar those reported in Steyerberg et al., 2008. Specifically, it was predicted that:

- Hypothesis 1a: The Core model would have statistically significant associations with the 6 month mortality and dichotomous GOS outcome, similar to those observed in Steyerberg et al., 2008.

- Hypothesis 1b: The addition of the Extended model sum score would contribute significantly to the core model and predict more of the variance in the 6 month mortality as well as in the dichotomous GOS.

Aim 2

Aim 2 sought to extend the findings of the IMPACT model and test its ability to measure a wider range of outcomes that have demonstrated ecological validity. To achieve this goal, the full range of the GOS (as opposed to the simple Favorable/Unfavorable dichotomy) and the DRS were used as outcome measures. It was hypothesized that:

- Hypothesis 2a: The IMPACT model would have a statistically significant association with the 6 month GOS such that poorer GOS scores would be related to a lower model Total score.

- Hypothesis 2b: The IMPACT model would have a statistically significant association with the 6 month DRS such that poorer DRS scores would be related to a lower model Total score.

- Hypothesis 2c: The IMPACT model would predict outcome on the DRS with more accuracy than it would on the full range of the GOS because of the level of detail and continuous range of the DRS.

Aim 3

Aim 3 sought to extend the IMPACT model by testing its ability to measure cognitive outcome in the domain of working memory at six months post injury. To achieve this goal, Digit Span would be used as the outcome measure and analyses would be controlled for level of education. It was hypothesized that:

- Hypothesis 3: The IMPACT model would have a statistically significant association with the 6 month Digit Span score after controlling for level of education such that poorer Digit Span total scores would be related to a lower model Total score.

CHAPTER 3
METHODS

General Methods

The current study utilized data from several studies, both ongoing and archival, across two research sites (University of Florida and University of Houston). The ongoing multi-site study (PI: Robiscek, University of Florida) funded by the National Institute of Health (NIH) seeks to systematically identify and validate a panel of biochemical markers for TBI (N= 79). It has been reviewed and approved by the Institutional Review Boards at both institutions. Additionally, archival data was used from several NIH funded studies conducted by Dr. Hannay, PhD at the University of Houston (N= 467).

Participants

A total of 546 participants were recruited from two Level-1 trauma centers: Ben Taub General Hospital in Houston Texas (N=503) and Shands at the University of Florida in Gainesville, Florida (N=43). Participants were patients who had sustained severe closed head injuries identified in the emergency departments or intensive care units of these hospitals. Patients who were or may have been pregnant were excluded from the studies. Patients were also excluded if they had an autoimmune disease, life threatening injuries in any organ system other than the head or spine, or a severe pre-existing chronic disease. Additionally, the studies excluded patients with a history of severe psychiatric conditions (e.g. psychotic disorders or bipolar disorder); however, patients with less severe conditions (e.g. depression or anxiety disorders) were not excluded. For the archival studies conducted at the University of Houston, patients 14 years old and older while the ongoing multisite biomarker study excluded patients under 18 years old. Patients were included if they had a severe TBI as defined by an

admission GCS of 8 or less. Additionally, in the ongoing multisite study of biomarkers, participants were included if they a ventriculostomy placed as part of their routine care, and had neuromonitoring probes for intracranial pressure.

Procedure

Consent for patient participation in the study was initially obtained from a legally authorized representative (LAR; typically a significant other or relative) as soon as possible upon the patients' arrival at the hospital. Consent was also obtained from someone close to the patient to participate in the study as a collateral source of information regarding the patient's background and pre-injury functioning as well as their functioning later in the recovery process. In this longitudinal study patients' abilities to consent for themselves were continually assessed based on the Galveston Orientation and Amnesia Test (GOAT; Levin et al., 1979). If patients were deemed capable of providing consent (based upon GOAT scores in the normal range 76-100) they were asked to do so.

Measurement of Physiological Predictor Variables

Methods for the collection of raw physiological data are presented below. This raw data was processed according to methods described following the explanations of how each variable was obtained.

Admission Glasgow Coma Scale (GCS) Motor Scale

For patient data collected at the University of Houston (N=503), the GCS was obtained post resuscitation of any hypotension or hypoxia but before surgery or other interventions. For patient data collected at the University of Florida (N=43) the post resuscitation GCS was ascertained through retrospective review of charts approximating as closely as possible the timing of the Houston data. For the purposes

of the IMPACT model used in this study only the motor scale was used consisting of 6 levels: (1) No response; (2) Abnormal Extension-Decerebrate Posture;(3) Abnormal Flexion-Decorticate Posture; (4) Withdraws from pain; (5) Localizes pain; and (6) Follows commands. The GCS exam was administered by a research nurse and observed by a research assistant. The exams were administered in a uniform way according to national guidelines for management of severe TBI (Badjatia et al., 2007). Regardless of the apparent neurological status of the patient, verbal directions were given first. If a patient was nonresponsive and unable to follow simple commands, a painful stimulus (pinch to inner arm or thigh, or nail bed pressure) was applied to induce a motor response in each limb not known to have paralysis.

Pupil Response

Pupil exam was performed post resuscitation. This was typically done by a physician or nurse as part of routine clinical exam by momentarily holding a flashlight over each eye individually. For the purposes of this study, constriction of pupil was recorded as present for both eyes, one eye, or neither eye.

Head CT Classification

Head CT scans taken on admission to the hospital as part of the patient's regular care were used in this study. All CT scans were read by a clinicians trained in neuroradiology. The Marshall CT classification system was used to classify the findings of the CT (see Table 3-1). Additionally, CT scans were examined for the presence of tSAH and EH. The characteristics of EH and tSAH were scored as present or absent, without further differentiation.

Table 3-1. Marshall computed tomographic classification

Category	Definition
I. Diffuse Injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
II. Diffuse Injury II	Cisterns are present with midline shift of 0-5 mm and/or lesion densities present; no high or mixed density lesion
III. Diffuse Injury III (swelling)	Cisterns compressed or absent (swelling) with midline shift 0-5 mm, no high or mixed lesion > 25 cc
IV. Diffuse Injury IV (Shift)	Midline shift > 5 mm, no high (shift) or mixed density lesion > 25 cc
V. Evacuated mass lesion	Any lesion surgically evacuated
VI. Non-evacuated mass lesion	High or mixed density lesion > 25 cc, not surgically evacuated

Hypoxia

Hypoxia was defined as any documented occurrence of a partial pressure of oxygen (pO_2) < 60 mmHg from time of injury until successful resuscitation. This was recorded as present or absent for the purposes of this study

Hypotension

The admission blood pressures were taken upon admission to the hospital and assessed for the presence of hypotension. Hypotension was defined as systolic blood pressure below 90 mm Hg (Butcher et al 2007). This was recorded as present or absent for the purposes of this study

IMPACT Model Sum Scores

As indicated above, the variables contained in the IMPACT Core and Extended models were used in proportional odds logistic regression analyses with the full range of GOS at 6-month post injury as the outcome measure. The regression coefficients from these analyses were rounded and scaled to create a weight for each of the variables in the model. These weighted scores (see Figure 3-1) were then added to yield a sum

score for the Core model and Extended model which were then added to yield an overall sum score for the model.

Figure 3-1. IMPACT model score chart for 6-month outcome after TBI

Characteristics	Value	Score (*b*)
Age (years)	≤ 30	0
	30 - 39	1
	40 - 49	2
	50 - 59	3
	60 - 69	4
	70 +	5
GCS Motor Score	None/extension	6
	Abnormal flexion	4
	Normal flexion	2
	Localizes/obeys	0
Pupil Response	Both pupils reacted	0
	One pupil reacted	2
	No pupil reacted	4
	Total Score Core Model	_____
Hypoxia	Yes or suspected	1
	No	0
Hypotension	Yes or suspected	2
	No	0
CT classification	I	-2
	II	0
	III/IV	2
	V/VI	2
tSAH	Yes	2
	No	0
EH	Yes	-2
	No	0
	Extended Model Subtotal	_____
	Total Score Extended Model	_____

For the current study, sum scores for the model were calculated from each participant's acute data. These weighted and summed scores were used as the independent variables in the analyses to follow rather than the raw values of the individual predictors. The regression coefficients used to develop the weights in the score chart were calculated based on the outcome measure of the GOS. These same weights will be applied to the raw predictors for the analyses of the other outcome measures of DRS and Digit Span. A new regression equation was developed for each

of the outcome measures tested. These analyses yielded R^2 values that told how much of the variance in the outcome measure was explained by the Sum scores from the IMPACT model. β weights for the IMPACT model score will also be obtained that will indicate how much an outcome score would change for each point increase in the IMPACT model Sum score. Ultimately, if these analyses were significant a clinician would be able to plug a patient's raw predictor values into the IMPACT score chart to yield a Total score that could then be put into a simple regression formula to calculate an estimated level of outcome as measured by the full GOS, DRS, or Digit Span.

The weights used in these analyses were applied to outcomes other than the one they were based on. Although several weaknesses to the this method have been cited (Rubin, et al., 1992), positive results obtained from hundreds of studies using this method suggest that it is robust to these limitations, much in the same way statistical methods can be robust to violations of some assumptions.

This methodology was justified because this study represents an attempt to take a powerful model based on a large sample and examine whether the same well validated model can be extended to predict different types of outcome with more specificity including measures with good ecological validity such as the DRS and measures with sound psychometric properties such as the Digit Span test. These methods have been used in similar studies (Charlson et al., 1994).

Additionally, it should be noted that the sample used in the analysis of Digit Span contained only those patients who survived six months, were functionally able to complete the Digit Span subtest and had available data on their level of education (N=76). This analysis again used the weights calculated from the IMPACT model

regression coefficients despite the fact that the samples differed in terms of the range of outcome included. This is justified because the sample used in the analysis for the current study represents a subset of the overall sample used in the IMPACT study. Therefore the prediction model should still apply to this truncated portion of the sample. These methods of applying a model to a subset of the original sample have also been used in other similar studies (Hemmelgarn et al., 2003; Sarbjit et al., 2005).

Measurement of Global and Cognitive Outcome

Outcome was assessed at 6 months post injury using the GOS, DRS and the Digit Span test. These different outcome measures were used to address different aims and hypotheses. Information to complete these measures was obtained from the patients and their families. Research assistants who obtained this information were extensively trained. The quality of the data collected was monitored in weekly sessions to determine the adequacy and reliability of the responses on these measures. If the research group did not agree that enough information had been obtained to accurately determine the DRS or GOS scores, additional data were obtained until a consensus was reached. The research assistants were in contact with the patients and their families when they were admitted to the study and maintained regular contact with the patients through the first six months post injury.

Additionally, a battery of neuropsychological tests including the Digit Span test (WAIS-III; Wechsler., 1997) was administered at six months post injury to those patients who were functioning at a level that permitted testing. Some patients completed the battery in an outpatient visit to the study hospital. If patients were unable to travel to the research hospital, efforts were made to travel to the patient. Others completed the tests as inpatients in a hospital or rehabilitation facility.

Global Functional Outcome Measures

Glasgow Outcome Scale (GOS)

The GOS is a five-point scale assesses outcome using 5 broad categories: (1) Death; (2) Vegetative State; (3) Severe Disability; (4) Moderate Disability; and (5) Good Recovery (Jennett and Bond 1975). The scale was developed as a means of standardizing outcome classifications across centers. This instrument is one of the most commonly used outcome measures utilized in neurosurgical studies of head injury outcome. For Aim 1 these scores will be grouped as Favorable (Moderate Disability and Good Recovery) and Unfavorable outcome (Death, Vegetative State, and Severe Disability) according to the methods of the IMPACT study. For Aim 2, all five categories were used for the analyses.

Disability Rating Scale (DRS)

The DRS is a 30-point scale (0 = no problems; 30 = dead) that is based on the sum of ratings on eight items that assess four areas: awareness/arousal, cognitive ability for self-care, level of physical dependence on others, and estimated ability for work, school, or homemaking activities (Rappaport et al., 1982). This instrument was developed to assess disability of severe head trauma patients from coma through different levels of awareness and functioning to community reentry. The raw score on this measure were used for the analyses in Aim 2.

Cognitive Outcome Measure: Digit Span

The Digit Span test from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler et al., 1997) is made up of two different tasks: Digits Forward and Digits Backward. For these tests the examiner reads random number sequences of increasing length aloud at the rate of one number per second. For the Digits Forward

test, the patient was asked to repeat each sequence exactly as it was given. These sequences ranged in length from 2 to 9 digits. For the Digits Backward task, patients were asked to repeat the digits exactly in reverse order. These sequences ranged in length from 2 to 8 digits. For both tasks, two trials are given of each span length and the subject received a raw score point for each correct trial. Testing is discontinued when the patient makes errors on both trials of a particular span length.

Although these tasks measure slightly different mental activities, they both correspond to the cognitive domain of working memory. This study is less concerned with the specificity of the underlying cognitive construct and more concerned with the sensitivity of the measure to brain injury. Therefore, the raw scores from each condition were combined to from one total score for this study's analysis to maximize the range of outcomes that will be achieved and minimize the floor effects that might have resulted from using just the backward span.

Analyses Utilized

Aim 1 Replication of IMPACT Core and Extended Models Predicting Mortality and Unfavorable Outcome on GOS

The first set of analyses will use mean, standard deviation, median and frequencies to describe data distribution. Univariate and multivariable forced entry logistic regression analysis will be used to examine the relative contributions of the Core and Extended IMPACT models to outcome prediction. The Total score of the Core model were used in the first block and the Total score of the Extended model were added in the second block with the scores as continuous variables and mortality at 6 months as the dichotomous outcome. Additionally, similar analyses were run with a dichotomized version of the GOS *Unfavorable* (Death, Vegetative State, or Severe

Disability) versus *Favorable* (Moderate Disability to Good Recovery) outcome at six months post injury as the dichotomous variable and the core and extended model scores again serving as continuous variables. The odds ratio (OR) and 95% confidence intervals (CI) were also calculated. One tailed p values less than 0.05 were considered to be statistically significant.

Aim 2 Extension of IMPACT Model Predicting Full GOS and DRS at Six Months

This set of analyses examined the extended IMPACT model using the full range of the GOS at six months post injury. The GOS is an ordered categorical variable and it cannot be justified to treat it as continuous. Therefore, these analyses used proportional odds ordinal logistic regression with the six month GOS as an ordinal outcome. This again involved logistic regression with the Total score of the Core model in the first block and the Total score of the Extended model added in the second block as continuous variables. The odds ratios (OR) and 95% confidence intervals (CI) were again calculated. Statistical analyses were performed running the SPSS 17 statistical package on a personal computer. One-tailed p values less than 0.05 were considered to be statistically significant. Nagelkerke's R^2 was calculated as an approximation to the percentage of the variability in the GOS that can be explained by the different levels of the model. Nagelkerke's R^2 was be used to measure the added predictive value of each level of the model.

For the second part of this aim, a multiple regression analysis was used to determine if the IMPACT model could predict outcome on the continuous DRS measure at six months post injury. For this analysis, the Total score of the Core model was entered in the first block and the subscore of the Extended model was added in the second block as continuous variables. The R^2 was used to measure the amount of the

variability in the DRS that can be explained by the model. One-tailed p values less than 0.05 were considered to be statistically significant. Finally, the R^2 from this analysis were compared to the Nagelkerke's R^2 to determine whether the DRS or GOS is better predicted by the models.

Aim 3 Extension of IMPACT Predicting Working Memory Outcome at Six Months

Finally, this set of analyses used the total Digit Span score as a continuous outcome measure to examine the proportion of the variance explained by the IMPACT model. This analysis used a multiple regression with the Core model score in the first block and the Extended model score added in the second block as continuous variables. Resulting R^2 statistics were reported to measure the amount of the variability in the Digit Span total score that could be explained by the model. One-tailed p values less than 0.05 were considered to be statistically significant. All statistical analyses were performed running the SPSS 17 statistical package on a personal computer.

CHAPTER 4
RESULTS

Sample Characteristics

A total of 546 patients were included in the present study. Demographic characteristics of the sample are presented in Table 4-1. Patients' ages ranged from 14-91 years, 83% were male, and the average education level was approximately 12 years. A higher proportion were Hispanic (42%) than White (36%), which is representative of the population demographics of the Houston area where much of the data was collected.

Table 4-1. Demographic characteristics of the sample (N = 546)

Characteristic	*N (%)*		*M*	*SD*	Range
Age			35.4	15.2	14-91
Education			11.8	2.6	3-20
Sex					
Male	453	(83.0)			
Female	93	(17.0)			
Race					
Hispanic	228	(41.8)			
White	196	(35.9)			
Black	111	(20.3)			
Asian/PI	11	(2.0)			

M = Mean, SD = standard Deviation

Table 4-2 presents the clinical characteristics of the current study sample as well as those included in the IMPACT study. Significant group differences were observed for several patient characteristics such that the current study sample generally showed more severe injury characteristics and had worse outcomes. The current study sample had more patients with no motor response (GCS=1) and fewer who demonstrated abnormal flexion (GCS=3) or withdrawal from pain (GCS=4). Additionally, the current study sample had more patients who exhibited higher levels of neurocognitive status (i.e., GCS=5 localization or GCS=6 obeying commands) than were present in the

IMPACT study sample. The present study sample also exhibited more severe injuries as characterized by pupil reactivity, as there were more patients with neither pupil responding and fewer with both pupils responding as compared to the IMPACT sample. Furthermore, the present study sample had more instances of hypoxia than the IMPACT sample. Regarding head CT characteristics, the present study's patients again showed more severe injuries as there were more instances of evacuated mass lesions (Marshall 5) and traumatic subarachnoid hemorrhages as compared to the IMPACT group with fewer patients who had no visible pathology (Marshall 1) or minor pathology (Marshall 2). In terms of outcome, the present study had a higher mortality rate (GOS=1), more patients rated as Severe Disability (GOS=3) and fewer patients rated as Good Recovery (GOS=5). In summary, the current study sample exhibited more severe injury characteristics and poorer resulting outcomes as compared to the IMPACT study.

Table 4-2. Patient characteristics of present sample and IMPACT study

	Characteristic		Present Study	IMPACT Study	*P*
			(n = 546)	(n = 8509)	
IMPACT Core Model predictors	Age, years: Median (25-75 %ile)		35 (25-46)	30 (21-45)	
	GCS Motor Score				
		None (1)	130 (24%)	1395 (16%)	<.001
		Extension (2)	70 (13%)	1042 (12%)	.692
		Abnormal flexion (3)	37 (7%)	1085 (13%)	<.001
		Normal flexion (4)	72 (13%)	1940 (23%)	<.001
		Localizes/obeys (5/6)	227 (42%)	2591 (30%)	<.001
	Pupillary reactivity				
		Both pupils reacted	323 (59%)	4486 (63%)	.003
		One pupil reacted	54 (10%)	886 (12%)	.698
		No pupil reacted	169 (31%)	1754 (25%)	<.001
IMPACT Extended Model predictors	Hypoxia				
		Yes or suspected	187 (34%)	1116 (20%)	<.001
	Hypotension				
		Yes or suspected	86 (16%)	1171 (18%)	.193
	CT classification				
		I	3 (1%)	360 (7%)	<.001
		II	154 (28%)	1838 (35%)	<.001
		III	120 (22%)	863 (17%)	<.001
		IV	9 (2%)	187 (4%)	.393
		V	231 (42%)	1435 (28%)	<.001
		VI	29 (5%)	509 (10%)	.521
	Subarachnoid hemorrhage (tSAH)				
		Yes	386 (71%)	3313 (45%)	<.001
	Epidural hematoma				
		Yes	73 (13%)	999 (13%)	.253

The 6-month post-injury outcomes for both samples are also presented in Table 4-3. In the current study sample, roughly two-thirds survived six months post injury, however only 36% of those were classified as having a Favorable outcome. The average DRS score was 14.2, which would be classified as Severe Disability (Rappaport, 1982). The standard deviation for this scale was 12.5 indicating a high level of variability in outcome in the current study sample.

Table 4-3. Patient outcomes of present sample and IMPACT study

	Characteristic	Present Study	IMPACT Study	*P*
		(n = 546)	(n = 8509)	
Outcome	Mortality			
	Survived	357 (65%)	6113 (72%)	.001
	Death	189 (35%)	2396 (28%)	.001
	6-month GOS			
	Favorable	196 (36%)	4427 (52%)	<.001
	Good Recovery	*98 (18%)*	*2761 (32%)*	<.001
	Moderate Disability	*98 (18%)*	*1666 (20%)*	*.351*
	Unfavorable	350 (64%)	4082 (48%)	<.001
	Severe Disability	*159 (29%)*	*1335 (16%)*	<.001
	Vegetative State	*2 (0%)*	*351 (4%)*	<.001
	Death	*189 (35%)*	*2396 (28%)*	<.001

Aim 1a Replication of IMPACT Core and Extended models Predicting Mortality

Logistic regression was used to model classification of mortality status based on IMPACT scores. The Core IMPACT model score was entered in the first block to determine its contribution to the prediction of mortality. The Extended IMPACT model score was then added to the second block to assess its added contribution to this model. The Core IMPACT model was significantly associated with mortality, with an increase of one point resulting in a 30% increase in the odds of mortality (OR = 1.30, 95% CI = 1.26-1.41; $p < .001$). Similarly, when the Extended IMPACT model score was added an increase of one point for these additional acute physiological predictors also results in a 30% increase in the odds of mortality when the Core IMPACT model score remains constant (OR = 1.30, 95% CI = 1.15-1.47; $p < .001$) (Table 4-4).

Nagelkerke R^2 statistics were calculated for the logistic regression models to estimate the amount of variance predicted by the models as a measure of goodness-of-fit (Nagelkerke, 1991). Nagelkerke's R^2 for the Core IMPACT model was 0.274 indicating that this score explained 27.4% of the variance in mortality after severe TBI in

this sample. The addition of the Extended IMPACT model score improved the predictive ability by 3.7 thus explaining 31.1% of the variance in patient mortality outcome.

Table 4-4. Logistic regression analysis for mortality (n = 546)

	B	SE B	Wald χ^2	*df*	*p*	Odds Ratio	95% CI
Step 1							
Constant	-2.213	.201	121.801	1	.000	.109	
Core	.259	.026	96.997	1	.000	1.30	1.26 – 1.41
Step 2							
Constant	-2.974	.287	107.372	1	.000	.051	
Core	.236	.027	77.641	1	.000	1.27	1.20 – 1.33
Extended	.264	.063	17.373	1	.000	1.30	1.15 – 1.47

Note: Step 1 R^2_N = .274, R^2_{CS} = .199; Step 2 R^2N = .311, R^2_{CS} = .225

The Core IMPACT model was able to differentiate survivors from non-survivors. Details of the correct classifications produced by the regression models are shown in Table 4-5. Sensitivity, defined as the proportion of deaths classified correctly by the regression model was 55% for the Core model while specificity, defined as the proportion of survivors classified correctly by the Core IMPACT model was 85%. The addition of the Extended IMPACT model reduced the sensitivity to 53% while specificity improved to 86%.

Table 4-5. Sensitivity and specificity of the IMPACT model for mortality prediction

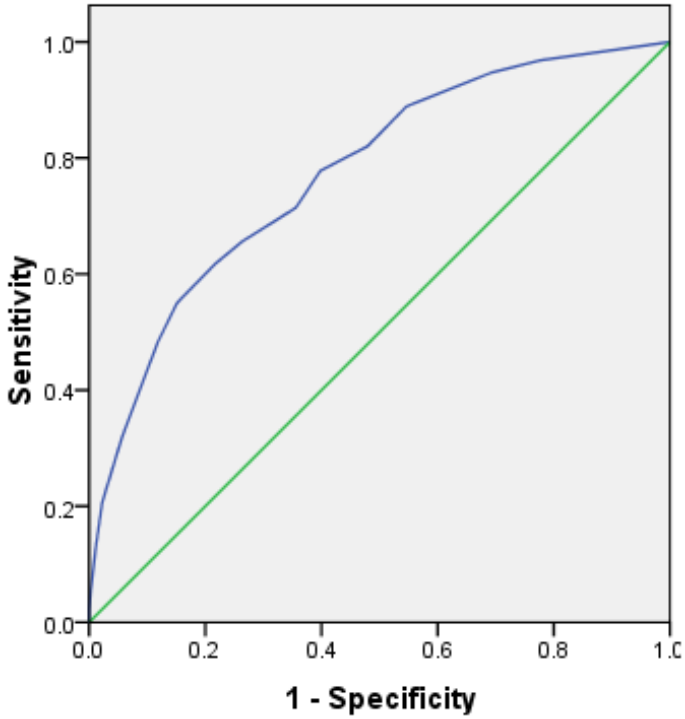
Outcome	Prediction Model	Sensitivity	Specificity
Mortality	Core	55%	85%
	+ Extended	53%	86%

The discriminative ability of the IMPACT model was examined by a receiver operating characteristic (ROC) analysis. Sensitivity and specificity values (expressed [1 – Specificity]) were plotted graphically to obtain ROC curves for each prediction model. Patients' scores were compared along their full range of cut-off points, and the measure

of the area under the ROC curve (AUC) was used as a quantitative indicator of the utility of the model to discriminate between survivors and non-survivors. As a point of interpretation reference, an AUC probability of 0.50 would indicate that the model fails to discriminate survivors from non-survivors, and a perfect test would have an AUC probability of 1.00 (Ritchie & Fuhrer, 1992).

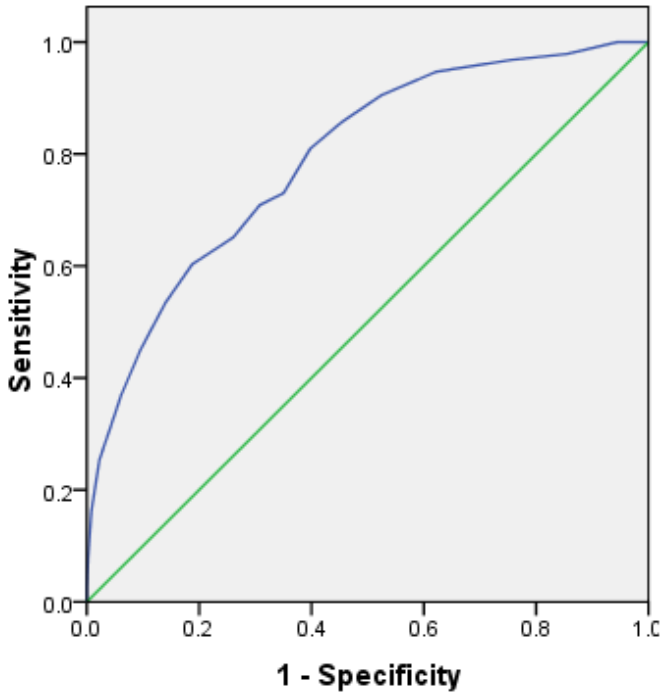
ROC curve analysis confirmed the discriminatory ability of the Core model for mortality (AUC 0.77). When the Extended model was added, the performance increased to 0.79 (Figure 1). ROC curves for both the Core model alone as well as with the addition of the extended score are presented in Figures 4-1 and 4-2. Adding the Extended model did not result in a significant improvement to the discriminative capabilities (AUCs) suggesting that CT and secondary injury variables contributed little to mortality prediction.

Figure 4-1. ROC curve for Core model predicting mortality



AUC = .773

Figure 4-2. ROC curve for Core + Extended model predicting mortality



AUC = .792

Aim 1b. Replication of IMPACT Core and Extended Models Predicting Unfavorable Outcome

Logistic regression was again used to model classification of Unfavorable outcome (based on GOS) using the Core and Extended IMPACT models as predictors. The Core IMPACT model score was entered in the first block with the Extended IMPACT model score added in the second block. The Core IMPACT model score was significantly associated with Unfavorable outcome, with an increase of one point resulting in a 33% increase in the odds of an Unfavorable outcome (OR = 1.33, 95% CI = 1.26-1.41; $p < .001$). An increase of one point to the Extended IMPACT model score resulted in a 30% increase in the odds of Unfavorable outcome (OR = 1.30, 95% CI = 1.17-1.49; $p < .001$) when the core model remained constant (Table 4-6). Thus, the Core and Extended IMPACT models showed the ability to predict Unfavorable outcome.

Nagelkerke's R^2 for the Core IMPACT model was .291 indicating that this score explained 29.1% of the variance in Unfavorable outcome after severe TBI in this sample. The addition of the Extended IMPACT model score improved the predictive ability of this model by 4%, explaining a total of 33.1% of the variance in patient outcome at this level of classification.

Table 4-6. Logistic regression analysis for Unfavorable outcome (n = 546)

	B	SE B	Wald	*df*	*P*	Odds Ratio	Confidence Interval
Step 1							
Constant	-0.78	0.16	25.25	1	.000	.46	
Core	0.29	0.03	96.45	1	.000	1.33	1.26 – 1.41
Step 2							
Constant	-1.51	0.23	41.45	1	.000	.22	
Core	.26	0.03	77.52	1	.000	1.30	1.23 – 1.38
Extended	.28	0.06	19.22	1	.000	1.32	1.17 – 1.49

Note: Step 1 $R^2_N = .291$, $R^2_{CS} = .212$; Step 2 $R^2_N = .331$, $R^2_{CS} = .241$

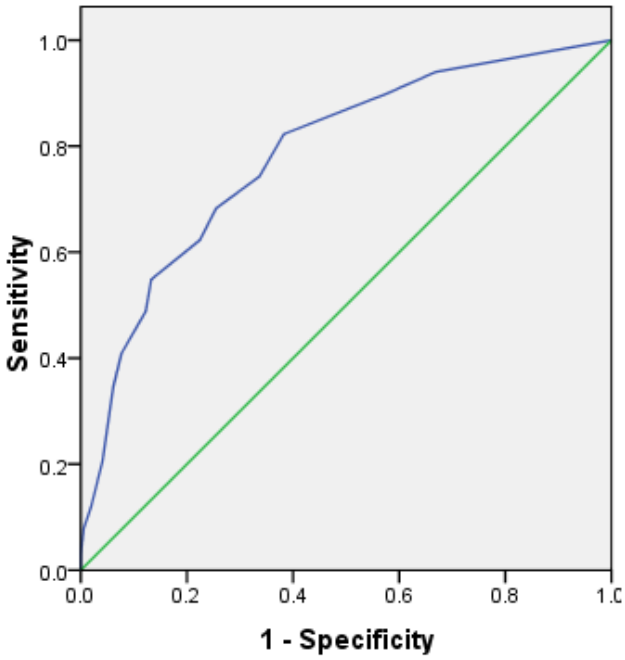
The Core IMPACT model was able to differentiate Favorable from Unfavorable outcomes. Details of the correct classifications produced by the regression models are shown in Table 4-7. The Core IMPACT model score correctly classified 82% of the patients with Unfavorable outcomes and 62% of those with Favorable outcomes. The addition of the Extended IMPACT model reduced the sensitivity to 81% while specificity remained at 62%.

Table 4-7. Sensitivity and specificity of the IMPACT model for Unfavorable outcome prediction

Outcome	Prediction Model	Sensitivity	Specificity
Unfavorable Outcome	Core	82%	62%
	+ Extended	81%	62%

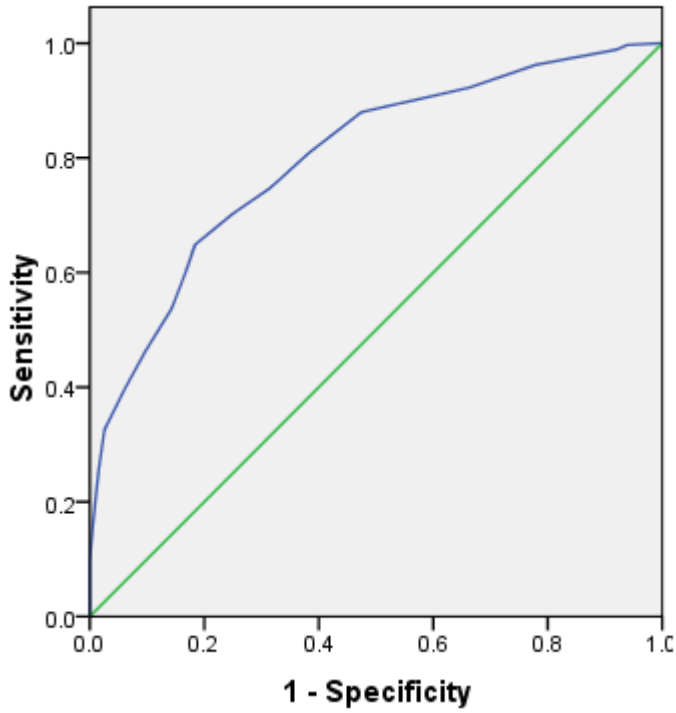
The discriminative ability of the IMPACT model for Favorable vs. Unfavorable outcome was again examined by ROC analysis. ROC curve analysis demonstrated that the Core and Extended IMPACT models showed discriminatory ability for Unfavorable vs. Favorable outcome (Figures 4-3 and 4-4).

Figure 4-3. ROC curve for the Core IMPACT model predicting Unfavorable outcome



AUC = .783

Figure 4-4. ROC curve for Core + Extended IMPACT model predicting Unfavorable outcome



AUC = .800

The IMPACT model score with the greatest classification value can be defined as the one with the greatest summed sensitivity and specificity values allowing for both predictive values to be equally emphasized. The sensitivity and specificity for various classification values of the Core and Extended IMPACT model scores are presented in Table 4-8. In this sample, there was no clear cut off score that maximized both sensitivity and specificity when predicting mortality. For the core model, it can be said that patients with scores lower than 6 are likely to survive while those with scores greater than 9 have a much poorer prognosis. The Extended IMPACT model showed that patients with IMPACT scores of less than 8 are likely to survive and those with scores lower than 6 will likely have a Favorable outcome.

Table 4-8. Sensitivity and specificity at the classification values of the IMPACT Core and Extended models for mortality and Unfavorable outcome prediction

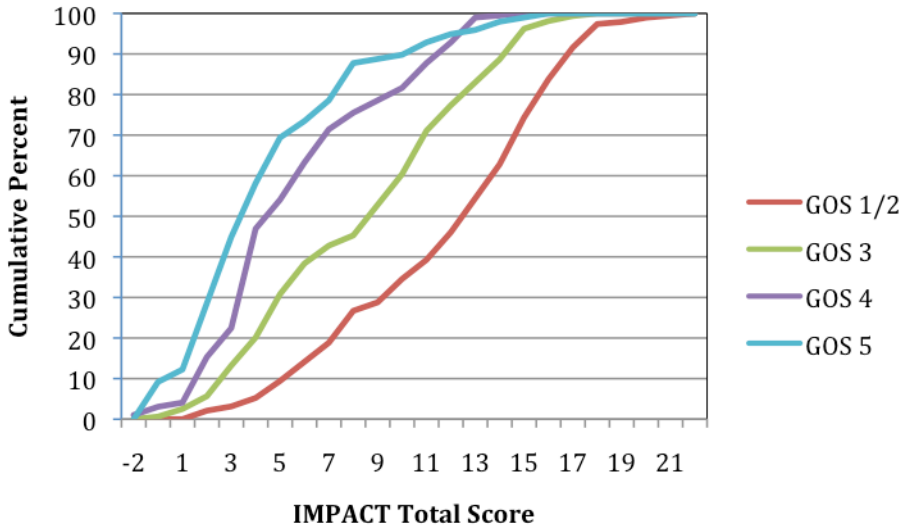
	Classification Values	Sensitivity (%)	Specificity (%)
Mortality			
Core	4.5	78	60
	5.5	71	64
	*6.5**	*66*	*74*
	*7.5**	*62*	*78*
	*8.5**	*55*	*85*
	9.5	48	88
Extended	6.5	86	55
	*7.5**	*81*	*61*
	8.5	73	65
	9.5	71	69
	10.5	65	74
	11.5	60	81
Unfavorable Outcome			
Core	1.5	90	43
	*2.5**	*82*	*62*
	3.5	74	66
	4.5	68	75
	5.5	62	79
	6.5	55	87
Extended	4.5	88	47
	*5.5**	*82*	*62*
	6.5	75	68
	7.5	70	75
	8.5	61	82
	9.5	60	83

Aim 2a Extension of IMPACT Model Predicting Full Range of Functional 6-month outcomes (GOS).

Before building the model, data was examined and plotted to visualize the ordinal regression model. In these analyses, the categories GOS=1 (Death) and GOS=2 (Vegetative State) were combined, because the percentage of patients in a vegetative state at 6-month post injury was low (0.4%). Figure 4-5 is a cumulative percentage plot of the IMPACT total scores with separate curves for each of the GOS levels. Figure 4-5 indicates that a larger percentage of patients with lower GOS scores had higher

IMPACT scores while a larger percentage of patients with higher GOS scores had low IMPACT scores. This shows preliminary evidence of a clear relationship between higher IMPACT model scores and more adverse GOS ratings. Moreover, the figure shows graphically that GOS scores of 4 and 5 are very close suggesting they will be difficult to distinguish from one another using the IMPACT model.

Figure 4-5. Plot of observed cumulative percentages IMPACT Core + Extended scores



Ordinal logistic regression analyses evaluated the IMPACT model total scores in their prediction of the full range of the GOS. The default Logit link function was used for these analyses. The IMPACT model significantly predicted GOS classification at six months $\chi^2(1) = 205.22$, $p < .001$. Nagelkerke's $R^2 = .34$, and the Test of Parallel lines was not statistically significant, suggesting that the parallel slopes assumption of ordinal regression was met. Table 4-9 presents the classification table resulting from this analysis, a matrix of the observed GOS classifications versus the values predicted by the statistical model. The model showed significant prediction of conscious survival (GOS 1-2 vs. 3-5) and Favorable outcome (GOS 1-3 vs. 4-5) at the threshold of Good

Recovery vs. less than Good Recovery the model was not significant indicating poor performance at this upper range of the GOS. Table 12 shows that 246 patients (45%) were classified into the correct GOS ratings based on model predictions; however, the model did not predict Moderate Disability (GOS=4). This again suggests that the IMPACT model performed poorly when predicting the upper range of GOS scores. Nevertheless, IMPACT scores were significantly and negatively associated with observed GOS classifications (see Table 4-10).

Table 4-9. Comparison of observed versus predicted categories in ordinal regression model using IMPACT total Score predicting GOS category

			Predicted GOS Category		
		Observed Classification	1 or 2	3	5
GOS	1+2	191	**125 (66%)**	56 (29%)	10 (5%)
	3	159	63 (40%)	**64 (40%)**	32 (20%)
	4	98	18 (18%)	34 (35%)	46 (47%)
	5	98	10 (10%)	31 (32%)	**57 (58%)**

N=546. The percentages listed in the table represent the predicted response/observed classification. Values in bold font highlight predictions that match the observed classification.

Table 4-10. Summary of ordinal regression of IMPACT total score predicting 6-month GOS

	B	SE B	Wald X^2	*Df*	*p*
GOS					
Conscious Survival vs. Death/VS	-3.04	.21	200.45	1	.000
Favorable vs. Unfavorable Outcome	-1.41	.18	65.00	1	.000
Good Recovery vs. Less than Good	-.23	.18	1.80	1	.180
IMPACT Total score	-.25	.02	168.40	1	.000

Nagelkerke R^2 = .34; p < .001

At the level of Good Recovery (GOS=5) versus less than Good Recovery (GOS=1-4), the ordinal regression of the IMPACT model was not significant. Sensitivity and specificity of the classifications into these GOS categories produced by the Core and Extended IMPACT models are shown in Table 4-11.

Table 4-11. Sensitivity and specificity of the IMPACT model for less than Good Recovery outcome prediction

Outcome	Prediction Model	Sensitivity	Specificity
Unfavorable Outcome	Core	0%	100%
	+ Extended	10%	98%

Sensitivity (defined as the proportion of patients with less than Good Recovery who were classified correctly by the regression model) was 0% for the core model while specificity (defined as the proportion of patients with Good Recovery classified correctly by the core model) was 100%. This indicates that the IMPACT model classifies all patients as having less than Good Recovery when analyzed at this threshold. Additionally, ROC curve analysis indicated that the classification scores that maximize the sensitivity and specificity of the model at this threshold were the same scores as those determined for the threshold of Favorable vs. Unfavorable outcome. This

indicates that the model of the model would classify the same patients at the two thresholds and suggests that this level of dichotomizing the patients gives no additional information. Taken together these results show that the IMPACT model cannot correctly distinguish between the higher GOS categories of Moderate Disability (GOS=4) and Good Recovery (GOS=5).

Table 4-12. Sensitivity and specificity at the classification values of the IMPACT Core and Extended models for Good Recovery prediction

	Classification Values	Sensitivity (%)	Specificity (%)
Good Recovery			
Core	1.5	79	59
	*2.5**	*74*	*66*
	3.5	67	72
	4.5	61	82
	5.5	54	82
	6.5	46	90
Extended	4.5	79	61
	*5.5**	*74*	*70*
	6.5	67	73
	7.5	61	79
	8.5	55	87
	9.5	52	88

Table 4-13 summarizes the performance of both the Core and Extended IMPACT models at each dichotomy of the GOS: Good Recovery (GOS 1-4 vs. 5), Favorable outcome (GOS 1-3 vs. 4-5), and Conscious survival (GOS 1-2 vs. 3-5), as well as with a proportional odds model, with their 95% confidence intervals. These results showed that the dichotomous odds ratios were remarkably consistent regardless of how the GOS was grouped. The slopes of all the regression lines were similar so the assumed common slope was used to obtain the proportional odds model. This implies that the proportional odds model gives an excellent summary of the association between the models and the GOS (McHugh et al., 2007). Thus the IMPACT model demonstrated a

significant relationship with the full range of GOS with stronger predictive ability at the lower range of ratings. As demonstrated previously, the findings regarding mortality and Unfavorable outcome are particularly robust. Thus it is likely that these results compensate for weaker performance at the threshold of Good Recovery when assessing the model for the entire range of GOS.

Table 4-13. Summary of proportional odds model for Core and Extended IMPACT model predicting GOS

	Core		*Extended*	
	OR	*(95% CI)*	OR	*(95% CI)*
Dichotomous OR				
Less than good versus Good Recovery	1.30	1.21 – 1.40	1.35	1.16 – 1.56
Unfavorable versus favorable outcome	1.33	1.26 – 1.41	1.32	1.17 – 1.49
Death/VS versus conscious survival	1.30	1.26 – 1.41	1.30	1.15 – 1.47
Proportional Odds	1.30	1.23-1.40	1.33	1.16-1.50

Aim 2b Extension of IMPACT model predicting DRS at six months

A linear regression was performed using DRS scores at 6 months post injury as the dependent variable and the IMPACT model total scores as independent predictor. Natural log transformations were performed on DRS scores to produce model residuals that were normally distributed. Table 16 presents the details of this regression analysis. As shown in the table, the IMPACT model was a significant predictor of DRS scores accounting for 32.0% of the variance [$F(1,544) = 256.02$, $p < .001$].

Table 4-14. Summary of hierarchical regression analysis with IMPACT scores predicting DRS scores

	B	*SE B*	*β*
Constant	1.04	0.08	
IMPACT	0.13	0.01	.57*

Note: R^2 = .320 (p < .001). * p < .001

After converting these figures back from the natural log transformation, the equation obtained was:

Disability Rating Scale score = 2.83 + (1.14)IMPACT Score

This suggests that each point increase in the IMPACT score results in a little over a point increase in DRS score.

Aim 2c Comparison of IMPACT prediction of GOS and DRS

The linear regression analysis of the IMPACT model and the DRS produced and R^2 of .320. The logistical regression for the model the model's prediction of the full range GOS scores produced a Nagelkerke's R^2 of .340 which is slightly higher but generally comparable. These results suggest that the IMPACT explains a similar portion of the variance with either of these functional outcome measures.

Aim 3 Extension of IMPACT Predicting Working Memory Outcome at 6-months

Table 4-15 presents the Digit Span characteristics of the present study sample. On average, patients who were able and available to complete this test performed within normal limits on both longest forward and backward spans (Lezak et al., 2004). These scores demonstrate that the majority of patients who were able to perform this task were able to do so within the range of normal performance.

Table 4-15. Digit Span scores of the current study sample (N=76)

Characteristic	*M*	*SD*	Range
Longest Forward Span	5.8	1.3	3-9
Longest Backward Span	4.1	1.4	0-7
Digit Span Total Score	12.5	4.6	3-25

For patients capable of performing some neuropsychological testing (n=76), a hierarchical regression analysis was performed using Digit Span total scores at 6 months post-injury as the dependent variable and using the IMPACT model total scores as an independent predictor. The continuous variable of total Digit Span score was normally distributed. Education was entered as an independent predictor in the first block to control for its contribution to performance on the Digit Span total score (Table 4-16). The percentage of variance explained by education was 10.6%. The IMPACT model scores did not contribute significantly to the model explaining only 2.7% of the variance in Digit Span performance.

Table 4-16. Summary of hierarchical regression analysis with education, IMPACT scores predicting Digit Span total scores (N=76)

		B	*SE B*	*β*
Step 1				
	Constant	5.41	2.65	
	Education	.64	.23	.33*
Step 2				
	Constant	6.86	2.83	
	Education	.62	.23	.32*
	IMPACT	-.21	.15	-.16

Note: Step 1 R^2 = .106 (*p* = .007); Step 2 ΔR^2 = .027 (*p* = *.163*). * *p* < .05

CHAPTER 5
DISCUSSION

Study Summary

The first aim of the current study was to replicate Steyerberg et al's IMPACT prognostic models of severe TBI predicting global outcome classifications of mortality and a dichotomous GOS classification of Favorable vs. Unfavorable outcome. The current study then sought to extend the findings of the IMPACT model by testing its ability to predict a wider range of more ecologically valid measures of outcomes using the full range of the GOS and the DRS rating scales. Finally, the current study sought to explore whether the IMPACT model could additionally predict cognitive outcome among survivors. More specifically, performance on Digit Span at 6 months post injury was used as a measure of cognitive outcome in the domain of working memory.

Several significant group differences in patient predictor characteristics were detected between the current study sample and the original IMPACT study (Steyerberg 2008). Overall, these differences showed the current study sample had sustained more severe injuries. This finding was expected given the restriction of the current study sample to patients with severe TBI while the IMPACT study included patients with moderate TBI as well. Regardless, for the differences that were detected, the percentages of patients with each predictor found in the present study sample fell within the range of percentages reported for the individual studies that were compiled to create the IMPACT database. Regarding outcomes for participants in the current study, the mortality rate was again within the range reported for the studies included in the IMPACT model and was consistent with previous research for patients with severe TBI (Hukkelhoven et al., 2003; Jennett et al., 1976; Murray et al., 1999; Nakamura et al.,

2006). In terms of the distribution GOS outcome found in the current study sample, a greater proportion of the patients died or had a Severe Disability at six months post injury with fewer having a Good Recovery for patients in the IMPACT study. Although these GOS outcome distributions were again statistically different from the IMPACT sample, the pattern and frequency were similar to those found in the research literature on specifically severe TBI (Thornhill 2000, Moppett 2000). The current sample DRS distribution showed that the mean outcome of the current study sample would be classified as a Severe Disability (Rappaport et al., 1998); however, there was a high level of variability as has been noted in the outcome literature for patients with severe TBI (Struchen et al., 2001; Pastorek et al., 2004). In terms of cognitive functioning the mean Digit Span scores in the current study sample fell below average but still within the normal range according to Lezak et al. (2004). The scores were commensurate with previous studies (Fork et al., 2005), and as Lezak et al. report it is not surprising to find a decrease in Digit Span scores in the first months following head trauma (2004).

Hypothesis 1

This study first sought to replicate the IMPACT prediction model findings of Steyerberg et al. (2008) and hypothesized that the IMPACT model would significantly predict the risk of mortality patients six months after severe TBI. The study findings supported this hypothesis and demonstrated that the combination of acute physiological variables in the IMPACT core model (including age, motor GCS, and pupil reactivity) can effectively discriminate between survivors and non-survivors at 6 months post injury. This finding is consistent with the some of the earliest prognostic models (Teasdale and Jennett, 1976; Jennet et al., 1976) as well as many years of subsequent research that show that these three common predictors create a robust prognostic

model for mortality prediction (Jain et al., 2008; Choi et al., 1983; Clifton et al., 1993; Hukkelhoven et al., 2005). This finding is further significant because it not only reiterates the predictive ability of these three commonly used predictors, but it also demonstrates that they retain the predictive ability when weighted and combined into a single composite score based on the IMPACT model. The results further showed that the addition of information regarding secondary injuries of hypoxia and hypotension as well as head CT characteristics in the IMPACT Extended Model further strengthened its predictive ability for mortality. The findings of the IMPACT models' predictive ability in the current study provide further external validation for the model.

To further replicate the IMPACT study, the current study hypothesized that the model could discriminate between patients who had Favorable outcomes (GOS ratings = 4-5) from those who had Unfavorable outcomes (GOS ratings = 1-3). The study findings confirmed this hypothesis for both the Core and Extended IMPACT models, with both demonstrating adequate discriminative ability between patients with Favorable and Unfavorable outcomes. The largest amount of prognostic information was contained in the Core model, but the Extended model did provide a small degree of additional prognostic value. The discriminative ability of the IMPACT model demonstrated in the current study was adequate and comparable to the findings of the original IMPACT study as a similar proportion of the variance in Unfavorable outcome was explained (Steyerberg et al., 2008).

Although several prognostic models have been created for TBI over the years, there has been little research regarding the generalizability of these models. The current study findings demonstrate generalizability of the IMPACT model across different

populations. Although the mean patient characteristics of the current study sample were still within the range reported for the studies the IMPACT patients were drawn from, they were in some cases significantly different from the means of the IMPACT study. As mentioned above, patients in the current study sample had more severe TBIs on average and were a more contemporary sample than the IMPACT studies (1995-2010 vs. 1984-1997). The fact that the IMPACT model demonstrated adequate discriminative ability despite these differences in sample characteristics speaks to the robustness of the prognostic model and its applicability to contemporary outcome prediction. However, current study suggests that the risk of adverse outcome after severe TBI has not improved significantly in the past decade. While this is a discouraging finding, it is consistent with other research (Stein et al., 2010; Moppet et al., 2000; Nakamura et al., 2006) and highlights the continued need for medical advances for this patient population.

Further analyses showed additional ways that the IMPACT model's ability to predict mortality and Unfavorable outcome could be useful for clinical and research purposes. The results showed that to maximize specificity and sensitivity an IMPACT classification value of 8 or greater can be used to identify patients at a high risk of Death and an IMPACT value of 6 or higher can be used to identify patients at a high risk of an Unfavorable outcome. These classification values could serve as ways to improve the classification of TBI severity or serve as cut-off points for the purposes of inclusion in clinical trials or research studies. Additionally, if applied appropriately, these scores could be useful in aiding with clinical decision-making. The IMPACT model with its web-based interface was intended to be an easy tool for clinicians to use predicting outcome

for their patients (Maas et al., 2008). However, studies have shown that this type of prognostic information has often been misused and implemented to make treatment-limiting decisions (Murray et al., 1993). While the sensitivity at these classification values is fairly high (81% and 82% respectively), this classification still commits type II error, which falsely classifies about 20% of patients as dying or having an Unfavorable outcome. Therefore, it should be emphasized as Steyerberg et al. argues, that these statistical models should only be used to augment and not replace clinical judgment (2008).

Hypothesis 2

The current study also sought to extend the findings of the IMPACT model and hypothesized that the IMPACT model could predict a broader range of outcomes as measured by the full range of the GOS. The results of the proportional odds model seem to confirm this hypothesis, as it was demonstrated that higher IMPACT model scores shift GOS classifications in an adverse direction for the entire distribution of GOS. An increase of one point in the total IMPACT score was associated with increasing the odds of adverse outcome by approximately 33% at each possible dichotomy of the GOS. However, further analyses showed that while the IMPACT model performs well when predicting lower ratings of GOS such as mortality and Unfavorable outcome, it demonstrated poorer predictive ability for the highest GOS rating of Good Recovery.

As discussed earlier the outcome dichotomy most commonly used in the severe TBI literature is Unfavorable (GOS = 1-3) and Favorable (GOS = 4-5). The IMPACT model performed best when this threshold was used to dichotomize the results. This is consistent with previous research that has shown acute prognostic models are

successful at discriminating at this threshold (Choi et al., 1983; Elf et al., 2002; Hukkelhoven et al., 2005). The model demonstrated poorer sensitivity when predicting Good Recovery vs. less than Good Recovery suggesting that the model is not as good at classifying patients with better outcomes. The model predicted almost all patients would fall below the threshold for Good Recovery. For this threshold, the sensitivity and specificity were optimal when using the same cut-off scores as indicated for the Favorable/Unfavorable dichotomy. This suggests that the model would make the same classifications of patients at either threshold and that the model could not adequately predict which patients would have a Good Recovery (GOS = 5). Therefore, the hypothesis that the IMPACT model would predict the full range of GOS was not confirmed. Patients in a Vegetative State (GOS =2) were grouped with non-survivors in the analyses, and the model did not show significant predictive ability for patients with Good Recovery. Thus, in terms of GOS ratings, the IMPACT model could only significantly predict mortality and Unfavorable outcome dichotomies as already demonstrated in previous analyses.

A further study hypothesis was that the IMPACT model would be able to predict to the full range of the DRS. This hypothesis was confirmed as the model accounted for 31.1% of the variance in DRS at 6 months post injury. This is a sizable portion of the variance in DRS scores and is significantly higher than has been found in previous studies using just individual acute variables to predict DRS scores at 6 months post injury (Struchen et al., 2001). Additionally, the findings showed that IMPACT model's ability to predict the full range of more detailed outcome as measured by the DRS was comparable to its ability to predict mortality and Unfavorable outcome. The Nagelkerke

pseudo R^2 estimates for the logistic regression analyses of mortality and Unfavorable outcome were .311 and .331 respectively, whereas the R^2 for the linear regression on DRS was .320. This suggests that when paired with an effective outcome measure that is collected appropriately and measures a range of outcomes, the IMPACT model can provide more information than was demonstrated in the Steyerberg et al study (2008). This provides further support that it is reasonable to use the combination and weighting of acute predictors in the IMPACT model as a single composite score when predicting functional outcome after TBI.

Hypothesis 3

Finally, this study sought to extend the Steyerberg findings even further and hypothesized that the IMPACT model would predict cognitive outcome (specifically working memory skills) after TBI. This hypothesis, however, was not supported, as the IMPACT model demonstrated little utility when applied to the basic cognitive test of Digit Span. The extension of the model to Digit Span did not show to be effective beyond what was predicted for these patients given their levels of education. This analysis may have suffered from decreased power as only 98 (18%) of the patients in the current study were available and able to complete the digit span test, and only 76 (14% of the total) of those patients provided information regarding their education level. Thus the majority of patients in the current study were unable to complete the Digit Span test due to a variety of reasons such as medical complications, being in an acute confusional state, being otherwise unresponsive or because they were unavailable. This caveat aside, the current finding of poor prediction of Digit Span performance is consistent with the finding that the IMPACT model demonstrated worse ability to predict Good Recovery on the GOS as compared to the lower ratings. With this weakness of the

model, it is unsurprising that it also struggles to differentiate among those with best outcomes in terms of their cognitive ability. This suggests that for more precise prediction of cognitive functioning after severe TBI, it is likely that an effective prognostic would have to include information beyond the acute physiological data.

There are likely to be many factors that contribute to some patients differentially retaining or regaining the cognitive abilities assessed by the Digit Span test at 6-months post injury. It seems likely that the variability observed among patients classified as having a Favorable outcomes are less a result of the acute injury severity and instead have more to do with post acute events and treatments, as well as interventions such as rehabilitation that take place after discharge from the hospital. This is a significant weakness of this study as none of this information could be taken into account. Thus the results suggest that the IMPACT model can predict whether a patient will have a Favorable outcome from the earliest time points. However, it appears that whether the patient will end up in the higher or lower ends of that range depends more on what happens during the six months that follows the injury rather than merely the status of the patient on the day of admission.

Implications

One application of the IMPACT model could be to offer a more precise classification of TBI than is traditionally provided from GCS scores alone. As evidenced by the current study sample and demonstrated in previous research, considerable heterogeneity can still exist in terms of admission characteristics and outcome among patients classified as severe TBI using primarily the GCS (i.e., GCS 3–8) (Hukkelhoven et al., 2003; Jennett et al., 1977; Murray et al., 1999; Nakamura et al., 2006). This heterogeneity muddles the picture for clinical and research purposes. Clinically, more

accurate classification could be used to better link a specific severity of injury with an appropriate therapeutic intervention. Additionally, a more accurate classification of severity may be used to better evaluate the efficacy of health care (both acute medical treatment as well as rehabilitation services) in TBI as outcome assessment could use targets that were more relevant to the initial injury severity. Clinicians could also use these predicted risk estimates as a method of measuring their efforts to continually improve their services and challenge themselves to obtain better results than predicted.

Similarly, more accurate classification of severe TBI patients according to their predicted risk could play an important role in designing research studies and clinical trials. Without a more accurate way to classify severe TBI, clinical trials must include patients with such poor prognosis that they will do poorly no matter how good the treatment is. Thus, inclusion of these worst of the patients with severe TBI simply decreases the statistical power of these studies (Califf et al., 1997). One noteworthy caveat to the use of this model to exclude patients from research studies and clinical trials is that the cut-off scores for the IMPACT model found in the current study (i.e., 6 for Unfavorable outcome and 8 for mortality) would likely exclude most older adults because ages over 60 already add 5 points to the overall score. Thus, the generalizability of these research studies and clinical trials to populations of older adults would be limited.

Overall, the current study highlights that use of the IMPACT model in early patient assessment could provide physicians with powerful prognostic information beyond mere predictions of mortality or Unfavorable outcome. This could be important for providing families and caregivers with more information about what to expect in

terms of recovery. Previous studies have reported that the majority of caregivers and family members want to be told as much information as possible regarding the patient's prognosis within the first 24 to 48 hours after injury (Shields, 1998). However, clinicians need to be aware of the limits and statistical uncertainty of this prognostic information and exercise care not to overemphasize the predictions when speaking with families, because this type of information is likely to be remembered (Carey et al., 2001). Armed with more information families can begin to prepare for the road ahead and learn what role they can play to best optimize the recovery of their loved one.

Study Strengths

A dominant strength of the current study is in the selection of outcome measures. The DRS provided a measure with a broad range of information that is still relatively easy to collect. Relatedly, this study benefited from strong methods of outcome measure collection, as both GOS and DRS ratings were rigorously quality controlled. While the current study was limited to use of the original GOS, future studies could validate and extend the findings using the structured interview version of the GOS or the Extended Glasgow Outcome Scale (GOS-E) to provide more breadth of potential outcomes and more structured means of measurement. Another important strength inherent in the current study was the variability of the sample including a distribution of races that included a significant proportion of Hispanic patients, as well as data collection that occurred across several years and across sites. This variability helped to demonstrate that the IMPACT is quite generalizable and still produces accurate predictions in spite of differences in settings, time periods, and ethnic groups.

Study Limitations

A limitation of the current study was the inconsistency in the collection of GCS information. The majority of the GCS ratings for the current study sample were obtained post resuscitation. In other words, GCS prediction values were within one hour of admission after doctors have indicated that hypoxia and hypotension are stabilized, but before any surgery or other interventions. However, a small number of the data points were gathered via chart review and were an approximation of this time point. While this is a weakness in the data, it still fits within the parameters of the IMPACT study and clinical applicability as this is a limitation inherent in this clinical setting. In order to improve the application of prognostic models that contain GCS information, these processes should be better standardized to gather the best possible acute data.

Finally, there was a high level of attrition for the collection of the cognitive outcome variable examined in this study. Therefore it is possible that a number of patients were capable of performing the Digit Span test, but were unavailable to complete it. Additionally, the data was incomplete in reporting whether any kind of impairments prevented the patients from completing this test. This information could be helpful to better characterize the sample and further explain these findings. Unfortunately, obtaining neuropsychological test data can be much more difficult than gathering functional outcome information (Clifton 1993).

Study Summary and Future Directions

The current study sought to replicate and extend a well-validated prognostic model of outcome after severe TBI (Steyerberg et al., 2008) and to examine its utility in predicting functional outcome on measures that capture a broader range of ability. The study showed that the IMPACT model has utility beyond predicting mortality and

Unfavorable outcome, especially the predictors are when paired with an outcome measure like the DRS that is scrupulously collected and controlled for data quality.

The model demonstrated weakness at the higher end of the functioning spectrum and failed to consistently and appropriately classify patients who had more favorable outcomes. Moreover the model showed limited utility when predicting cognitive working memory ability 6 months after injury. These findings indicate the model remains useful as an acute predictor composite, but they suggest that other variables would likely contribute more to models of prediction among patients with better outcomes.

Future studies should examine the model's utility in combination with post acute measures such as protein biomarkers, MRI, and the same physiological variables it measures acutely, through the post acute phase. As the higher functioning patients progress in their recovery, predictions of finder detail outcome (e.g., cognitive) become more urgent for discharge placement and family planning. Therefore, studies that tested the IMPACT model along with additional data on post-acute physiological events and treatment as well as discharge placement variables regarding rehabilitation services would likely provide more information regarding which patients have the best chance of a full recovery.

Nevertheless, the current model shows promise for creating more precise classifications of injury severity to help reduce the heterogeneity among severe TBI patients for research purposes and clinical trials. Future studies should examine the properties of this model for this purpose of proposing sub-classifications. From a clinical standpoint, more precision in severe TBI classification could provide a much more accurate snapshot than is currently available which would enable quicker responses

and better exchange of information among physicians. The IMPACT model could provide a powerful tool to communicate information among clinicians and to patient's families.

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BIOGRAPHICAL SKETCH

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