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Matthew M. Gregory Date

Predicting Favorable Outcome in Patients who Exhibit a Normal CT Scan after Moderate or Severe Traumatic Brain Injury

By:

Matthew M. Gregory
Master of Public Health (MPH)

Department of Biostatistics and Bioinformatics

_____

Dr, Reneé H. Moore, PhD
Thesis Advisor

_____

Dr, Jonathan J. Ratcliff, MD, MPH
Thesis Reader

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Predicting Favorable Outcome in Patients who Exhibit a Normal CT Scan after Moderate or Severe Traumatic Brain Injury

By Matthew M. Gregory

A *post hoc* analysis of clinical trial data from the Progesterone for Traumatic Brain Injury Experimental Clinical Treatment (ProTECT III) clinical trial was conducted in an effort to elucidate patient characteristics that could be used to predict 6-month patient outcome as defined by an Extended Glasgow Outcome Scale stratified dichotomy. Patients in this trial were diagnosed with a moderate or severe traumatic brain injury (TBI) upon inclusion. Univariate analysis and multivariable logistic model selection was performed on the potential patient characteristics to create a prediction model for 6-month patient outcome in both the entire cohort of clinical trial patients (N = 829) as well as the cohort of patients who exhibited an initially normal CT scan (N = 105). An assessment of efficacy of the progesterone treatment was also conducted for the normal CT cohort of patients. Similar to the results of the randomized clinical trial, progesterone treatment was again not associated with the 6-month dichotomized outcome (OR: 0.571 (0.227, 1.437)) in the normal CT cohort of patients. Patient characteristics that were found to significantly predict patient outcome in the entire cohort include verbal GCS score, CT scan, age, ISS, and whether or not the patient underwent a prior TBI, non-intraventricular ICP monitor installation or ventriculostomy. In the cohort of patients with a normal CT scan, verbal GCS score, blood glucose concentration, and pupil response were found to significantly predict patient outcome at 6 months.

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Acronym Key

AIS – Abbreviated Injury Scale

CT – Computed Tomography

GCS – Glasgow Coma Scale

GOS – Glasgow Outcome Scale

GOS-E – Extended Glasgow Outcome Scale

ICP – Intracranial Pressure Monitoring

ICU – Intensive Care Unit

INR – International Normalized Ratio

ISS – Injury Severity Score

PEG – Percutaneous Endoscopic Gastrostomy

ProTECT – Progesterone for Traumatic Brain Injury Experimental Clinical Treatment

TBI – Traumatic Brain Injury

Introduction

Contributing to almost a third of all injury-related deaths in the United States alone, traumatic brain injury (TBI) is a major public health concern. According to the United States Centers for Disease Control and Prevention, every year during 2002 to 2006 it was estimated that 1.7 million TBI-related injuries occurred in the United States, leading to approximately 1.4 million emergency department visits, over 275,000 hospitalizations and an astounding 52,000 deaths.[1] Direct and indirect TBI-related costs associated with medical treatment, work loss, and loss of life range from $51.2 billion to over $221 billion annually.[2-6] Both globally and in the United States, incidence of TBI-related injuries is on the rise due to a range of factors. In developing countries, there is a sharp increase in the use of motor vehicles.[7] Consequently, there has been a sharp increase in motor vehicle accidents resulting in TBI-related injuries – so much so that the World Health Organization estimates that traffic-related accidents will be the third largest cause of global burden of injury and disease by 2020.[7] In the United States and other developed countries, the rise of the baby boomer generation into advanced age is leading to an increase in TBI-related injuries associated with falls.[8]

While much progress has been made understanding the mechanisms surrounding TBI-related injuries, research focused on acute TBI neuroprotection strategies have proven to be less than successful. Over twenty pharmaceutical agents have been tested through well-designed randomized clinical trials over the last 35 years with none of these agents proving to be efficacious in the treatment of TBI.[8] One potential barrier in finding an effective TBI treatment intervention is associated with the inherent heterogeneity of the injuries and the appropriate identification and classification of patients who would most appropriately respond to treatment.[9-12] During this time, many tests, classification schemes, and prognostic tools have

been developed in an attempt to further classify these traumatic brain injuries.[13-16] One particular procedure that has been universally implemented and widely utilized in examining and classifying TBI patients is computed tomography (CT) scans.[17] First utilized in the 1970s, millions of these brain CT scans are performed each year in emergency departments around the world.[18] Due to its wide availability and high reliability, this procedure, performed after stabilization of the respiratory and cardiovascular systems, is the premiere diagnostic tool used to detect life-threatening abnormalities in the brain that may require immediate intervention.[19]

A CT scan is a noninvasive procedure that makes use of a combination of x-rays, taken at various angles around the object of interest, to produce cross-sectional images or slices of the object. Therefore, a brain CT has great clinical utility and highlights multiple TBI injury patterns including subarachnoid hemorrhages (SAH), cerebral contusions, intraparenchymal hemorrhages, subdural hematomas (SDH), epidural hematomas (EDH), intraparenchymal hematomas, as well as focal and diffuse patterns of axonal injuries.[9, 19] These injuries can be further described by factors such as location and extent of injury. In an attempt to classify these injuries, Marshall et al. developed a 6-point CT classification scale for TBI patients based on the type and severity of the abnormalities from the CT scan in 1991 (Table 1).[10] Since its implementation, this scale has been widely utilized as a significant predictor of TBI outcome. However, recent studies have illustrated the need to further expand the Marshall score to utilize other CT characteristics such as subarachnoid hemorrhages and further differentiating mass lesions and basal cisterns.[21] As a result, the Rotterdam score was created in 2005 to serve as a more comprehensive prognostic tool for TBI and is now equally as utilized (Table 2).

Table 1. The Marshall Score is used to classify CT results of patients with a traumatic brain injury.

Marshall Classification	Description[3,21]
Diffuse Injury I	No visible intracranial pathology on CT scan
Diffuse Injury II	Cisterns present with midline shift of 0-5 mm and/or lesions densities present; no high or mixed density lesion >25 cm^3 (may include bone fragments and foreign objects)
Diffuse Injury III	Cisterns compressed or absent with midline shift of 0-5 mm; no high or mixed density lesion >25 cm^3
Diffuse Injury IV	Midline shift >5 mm; no high or mixed density lesion >25 cm^3
Evacuated Mass Lesion	Any lesion surgically evacuated
Non-Evacuated Mass Lesion	High or mixed density lesion >25 cm^3; not surgically evacuated

Table 2. The Rotterdam Score was developed to supplement the Marshall Score in an attempt to further classify CT results.

Rotterdam Score	Description[21]
Basal Cisterns	
0	Normal
1	Compressed
2	Absent
Midline Shift	
0	No shift or ≤ 5 mm
1	Shift > 5 mm
Epidural Mass Lesion	
0	Present
1	Absent
Intraventricular Blood or Traumatic SAH	
0	Present
1	Absent

In addition to these prognostic tools associated with the CT scan, a variety of other classification schemes have been developed and are concurrently utilized to classify TBI. One of

the most widely-used scoring systems in the assessment of TBI unconsciousness is the Glasgow Coma Scale (GCS). Developed in 1974, this easy-to-perform assessment has been widely adopted and is a reliable tool used to describe the severity of acute TBI – since its inception, over 10,000 published articles have made use of it to classify TBI-related injuries. The GCS is composed of three components that are individually scored based on responses to external stimuli: the eye, verbal, and motor sub-scores (Table 3). The sum of the three individual scores yield the GCS score, with a range of 3 to 15. By convention, a score of 13-15 is classified as mild TBI, while a score of 9-12 is classified as moderate TBI, while a score of 3-8 is classified as severe TBI. If a patient has been intubated, which is a procedure that involves inserting a tube into a patient's airway to assist with breathing, only the motor component of the GCS score is used.

Table 3. The Glasgow Coma Scale is used to evaluate severity of traumatic brain injury. The values of the three components are summed to get a total score. A sum of 3-8, 9-12, and 13-15 signify mild, moderate, and severe injury respectively.

GCS Subscore		Description
eye		
	4	spontaneous movement
	3	movement when commanded
	2	movement when subject to pain
	1	none
verbal		
	5	oriented
	4	confused
	3	inappropriate
	2	incoherent
	1	none
motor		
	6	obeys commands
	5	localizes pain
	4	withdraws from pain
	3	flexes to pain
	2	extends to pain
	1	none

Clinical practice guidelines advise that patients who exhibit a normal CT scan and a normal clinical exam after head trauma may be discharged from the emergency department in the absence of other injuries. However once discharged, these patients don't necessarily exhibit a good outcome on follow-up. Counterintuitively, patients with a normal CT are sometimes diagnosed as having a moderate or even severe TBI via the GCS, indicating some larger underlying problem not being detected by CT. One shortcoming of CT imaging is that it is not able to detect diffuse microscopic injury in the white matter of the brain. In an effort to properly treat and appropriately discharge these patients to ensure they will have the best outcome possible, a considerable amount of research has been conducted attempting to link CT findings with patient outcome. Much of this research has been conducted on cohorts of patients that have been classified with mild TBI via the GCS. These studies have almost universally shown that the GCS score coupled with the normal CT scan and the absence of other clinical issues sufficiently predict a good outcome.[22, 23] Other studies have found that the vast majority of patients that experience a TBI do not display symptoms via the CT scan; one particular study of the patients that exhibited an initial GCS score of 15 showed only 5% had trauma-related CT abnormalities.[24,25] As a result, the study continued to argue that CT scan was not a valid predictor of outcome and therefore, more sensitive measures are needed to detect abnormalities.[26]

Recently, research has been undertaken in an effort to include patients with head injuries of all severity. A 2014 study investigating the necessity for continued monitoring of TBI patients with negative head CT concluded that the probability of delayed complications was negligible for these patients. Interestingly, this same study accounted for a cohort of normal CT individuals with a GCS between 3 and 12 as being attributed to non-traumatic intracranial lesions, alcohol and substance abuse, comorbid acute and chronic health problems, and sedation due to other

non-cerebral injuries.[27] Additional research, performed to test the possibility of predicting CT abnormalities via the GCS score, determined that the use of GCS score was not sufficient for assessing the level of injury of mild, moderate and severe TBI patients and therefore advocated for a better set of scoring systems.[28] Others have recommended a new classification scheme that accounts for both the GCS score and the results from the initial CT scan as a means to appropriately give care.[29] With regards to outcome prediction, recent research by Yuh et al. has demonstrated the effectiveness of utilizing quantitative CT features to predict patient outcome at 6 months.[30] Another study conducted in Europe concluded that a poor 6 month outcome was associated with a low GCS, a variety of CT abnormalities such as basal skull fracture, traumatic subarachnoid hemorrhage, and subdural hematoma, and lesion type.[31]

While a large number of studies are associated with assessing the relationships between GCS score and CT outcome, GCS score and patient outcome, and CT outcome and patient outcome, no research has been presented that investigates the three taken together. Therefore, is thesis strives to add to this extremely limited body of literature of predicting patient outcome in TBI patients who are classified as having a moderate or severe TBI as classified by the GCS yet exhibit a normal CT scan upon arrival into the emergency department.

Methods

Clinical Trial Description and Results[32]

This analysis is a retrospective *post hoc* examination of clinical trial data from the Phase III randomized, double-blinded, placebo-controlled Progesterone for Traumatic Brain Injury Experimental Clinical Treatment (ProTECT III) clinical trial that was conducted from 2010 to 2013. This trial sought to determine the efficacy of an intravenous progesterone treatment in the early stages of TBI intervention. Conducted at 49 trauma centers across the United States, this trial was funded by the National Institute of Neurological Disorders and Stroke (NINDS) and was conducted through a NINDS-funded network of 22 academic medical center hubs each with their own respective sites.

Utilizing a stratified dichotomy of the Extended Glasgow Outcome Scale (GOS-E) score at 6 months after injury, the clinical trial ultimately yielded a null finding; there was found to be no significant difference between the progesterone treatment group and the placebo group in the proportion of patients yielding a favorable outcome (RR = 0.95, CI_{95}: [0.85, 1.06], p-value = 0.35). Possible explanations for the failure of efficacy included heterogeneity of disease, potential confounding pre-existing conditions, and characteristics of individual patterns, which were heavily-controlled for in the animal studies, yet proved to be too large of a role to overcome in human subjects.[32]

Progesterone Intervention

The purpose of the clinical trial was to assess the efficacy of progesterone as a treatment for TBI-related injuries. Progesterone, an endogenous steroid synthesized in the central nervous system, has been shown to exhibit neuroprotective effects in four different animal species by 20

independent research groups.[33] Additionally, preclinical evidence has suggested that the hormone was effective in initiating a variety of biological processes in the brain such as reducing cerebral edema and neuronal atrophy, enhancing the blood brain barrier, intensifying remylination of the neurons, and protecting against motoneuron degeneration and neuroinlfammation.[34-39] In addition, a pair of Phase II clinical trials showing evidence of the progesterone treatment leading to better functional recovery and lower mortality were conducted.[40-41] Based on the consistently promising results of the animal studies, the preclinical trial studies, and the phase II clinical trial results, ProTECT III was established and designed in the hopes of definitively testing the efficacy of progesterone on patients with moderate and severe blunt TBI injuries.

Drug kits consisting of both the progesterone and placebo treatments were prepared. Each solution was prepared by combining a weight-based dose of a specific concentration (0.05 mg of progesterone per kilogram of body weight per milliliter of infusate) with a sufficient volume of fat-emulsion (Intralipid 20%, Fresenius Kabi) to reach 250 mL. Patients enrolled in the study were administered the treatment in three doses: a one-hour loading dose, a 71-hour maintenance dose, and finally 3 eight-hour taper doses (totaling a 24 hour taper infusion). An intravenous catheter was used to administer the treatment at 14.3 mL per hour for one hour, 10 mL per hour for 71 hours, 7.5 ml per hour for eight hours, 5.0 mL per hour for eight hours and 2.5 mL per hour for eight hours, totaling a full 96 hours of total treatment time.

To maintain the integrity of the clinical trial, both the patients and the administrators of the treatment solution were blinded to the identity of the treatment. The placebo control that was utilized in the trial was ethanol.

Participants & Randomization

A total of 882 patients were subject to randomization, out of the pre-planned sample of 1140, before recruitment was halted and the trial was concluded based on interim O'Brien and Fleming efficacy and futility analyses that failed to prove efficacy of the progesterone treatment.[32] Subjects included in this analysis were adults who had been subject to a blunt mechanism TBI, a brain injury involving physical trauma in which the patient's head is being struck or strikes an object, with an initial GCS of 4 to 12, indicative of moderate to severe TBI. In addition, patients were enrolled only if treatment could be initiated within four hours of the injury.

As alluded to in the introduction, patients enrolled in the study immediately underwent a CT scan to assess neurological abnormalities. An independent radiologist assessed each CT image and carefully documented any findings indicative of an abnormality. Primary abnormalities of concern included epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intra-ventricular hemorrhage, intraparenchymal hematoma, brain contusion, diffuse axonal injury, and cranial fractures. The radiologist also noted the presence of increased intracranial pressure, cerebral edema, and localized swelling. All but one of the ProTECT patients were found to have undergone an initial CT scan and were therefore included in the analysis (N = 881).

Additional patient exclusion criteria for this analysis was based on the exclusion criteria for the ProTECT III clinical trial. These criteria included if the patient was in an unsurvivable injury; if cardiopulmonary resuscitation was administered; the patient exhibited signs of hypoxemia, hypotension, spinal cord injury, or status epilepticus; the patient had unresponsive bilateral dilated pupils; the patient was pregnant, a prisoner of the state, severely intoxicated (

[ethanol] ≥ 249 mg/dL), had reproductive cancer, had an allergy to progesterone or the fat emulsion vehicle used to administer the progesterone, had a blood clotting disorder, had active myocardial infarction, ischemic stroke, pulmonary embolism, deep-vein thrombosis, were on an opt-out registry, or wearing an opt-out bracelet (Figure 1).[32]

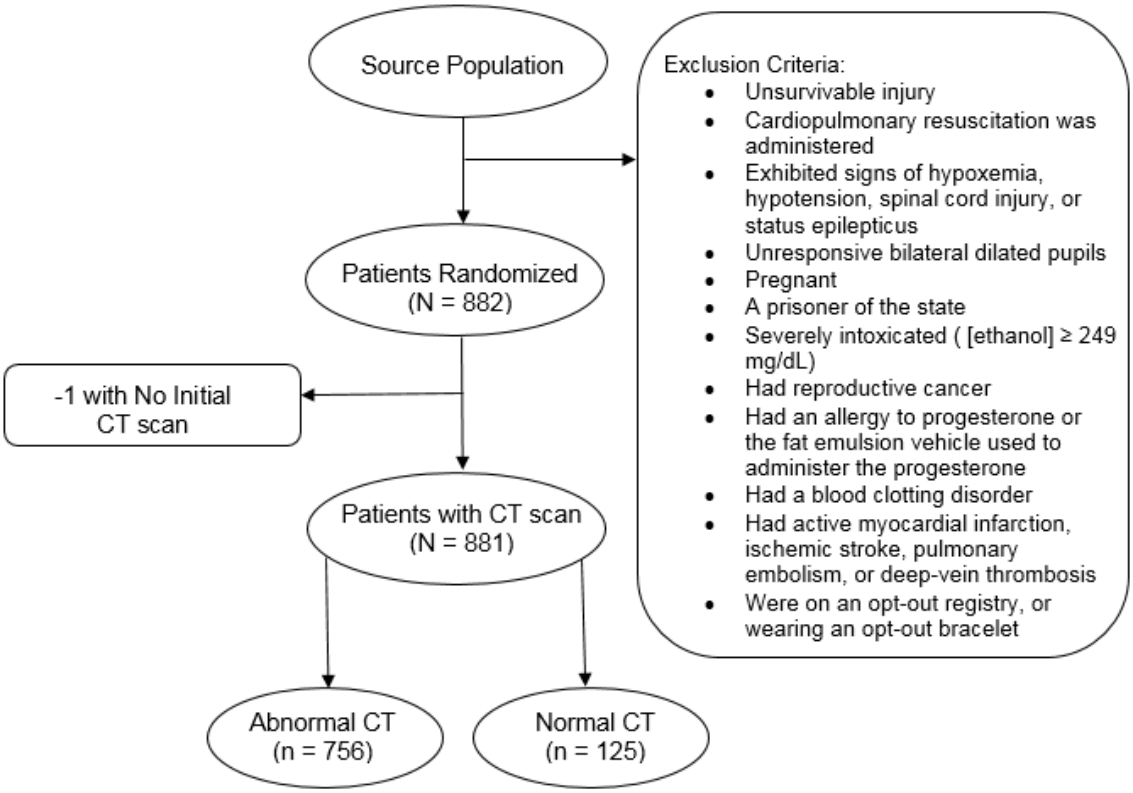

Figure 1. Study sample diagram detailing the exclusion criteria of the ProTECT III clinical trial stratified by CT scan.

Patients were randomized on treatment group to either the progesterone or placebo treatment arm. Randomization was additionally performed using the minimization and biased-coin flip algorithms to ensure that each arm was balanced with respect to initial injury severity, sex, age, and enrollment site.

Data Collection

Data were collected by local teams of researchers at the respective trauma centers. Rigorous training sessions and constant quality assessment ensured that consistent scores were applied to potential subjective tests when applicable. Data related to serious adverse events and clinical transgressions were reported and collected throughout each patient's duration of the study (i.e., 6 months). Information on all adverse events was collected and compiled within one week of the patient being admitted to the study.

Outcome Measure

The primary outcome of interest in both the clinical trial and this analysis was whether or not the patient exhibited functional recovery as determined by a binary version of the Extended Glasgow Outcome Scale. This eight point scale (Table 4), developed in 1981, is based on one of the original assessment scales for TBI outcomes called the Glasgow Outcome Scale (GOS). Developed in 1975, the GOS is a five point scale that evaluates patient status into one of the following categories: dead, vegetative state, severe disability, moderate disability, and good recovery.[42] While the GOS scale was transformative in simplifying patient outcomes into a manageable form, many felt that the score was too restrictive. With the development of the GOS-E score, each stage of conscious survival was subdivided into two categories yielding the eight point Extended Glasgow Outcome Scale (GOS-E).[43]

Table 4. The Glasgow Outcome Scale and Extended Glasgow Outcome Scale used to evaluate TBI patient outcome.

GOS Score	GOS-E Score	Outcome[43]
1	1	Death - when death occurs
2	2	Vegetative State - unawareness with only reflex responses with brief episodes of spontaneous eye opening
3	3	Lower Severe Disability - dependent upon daily support for mental and/or physical disability AND cannot be left alone for more than 8 hours at a time
	4	Upper Severe Disability - dependent upon daily support for mental and/or physical disability AND can be left alone for more than 8 hours at a time
4	5	Lower Moderate Disability - some disability (e.g., aphasia, hemiparesis, epilepsy and/or deficits of memory or personality) but are independent at home even if they are dependent outside the home AND are not able to return to work
	6	Upper Moderate Disability - some disability (e.g., aphasia, hemiparesis, epilepsy and/or deficits of memory or personality) but are independent at home even if they are dependent outside the home AND are able to return to work in some capacity
5	7	Lower Good Recovery - resumes normal life with ability to work (not necessarily to pre-injury status) with some minor neurological and psychological debilitating deficits.
	8	Upper Good Recovery - resumes normal life with ability to work (not necessarily to pre-injury status) with some minor neurological and psychological non-debilitating deficits.

While there are a variety of methods that can be implemented that utilize the GOS-E score, the method that was chosen for this analysis made use of a stratified dichotomy of GOS-E scores that further integrated the initial severity of the injury. Patients with a less severe initial injury had to have a better recovery than those patients with more severe initial injury diagnoses (Figure 2). For example in patients who were diagnosed with moderate TBI injury, a favorable outcome was considered if the patient was evaluated with a 6-month GOS-E score of 7 or 8, while in patients diagnosed with a moderate to severe or severe head injury, a favorable outcome was considered if a 6.month GOS-E score of ≥ 5 and ≥ 3 was attained respectively. This

approach was utilized to not only account for the ordinal nature of the GOS-E score but also to appropriately handle the inherent unevenness associated with the scale of the outcome measure and account for the various severities of injury. For example, the difference between a GOS-E score of 1 (dead) and 2 (vegetative state) is different from the difference between a score of 7 (lower good recovery) and 8 (upper good recovery).

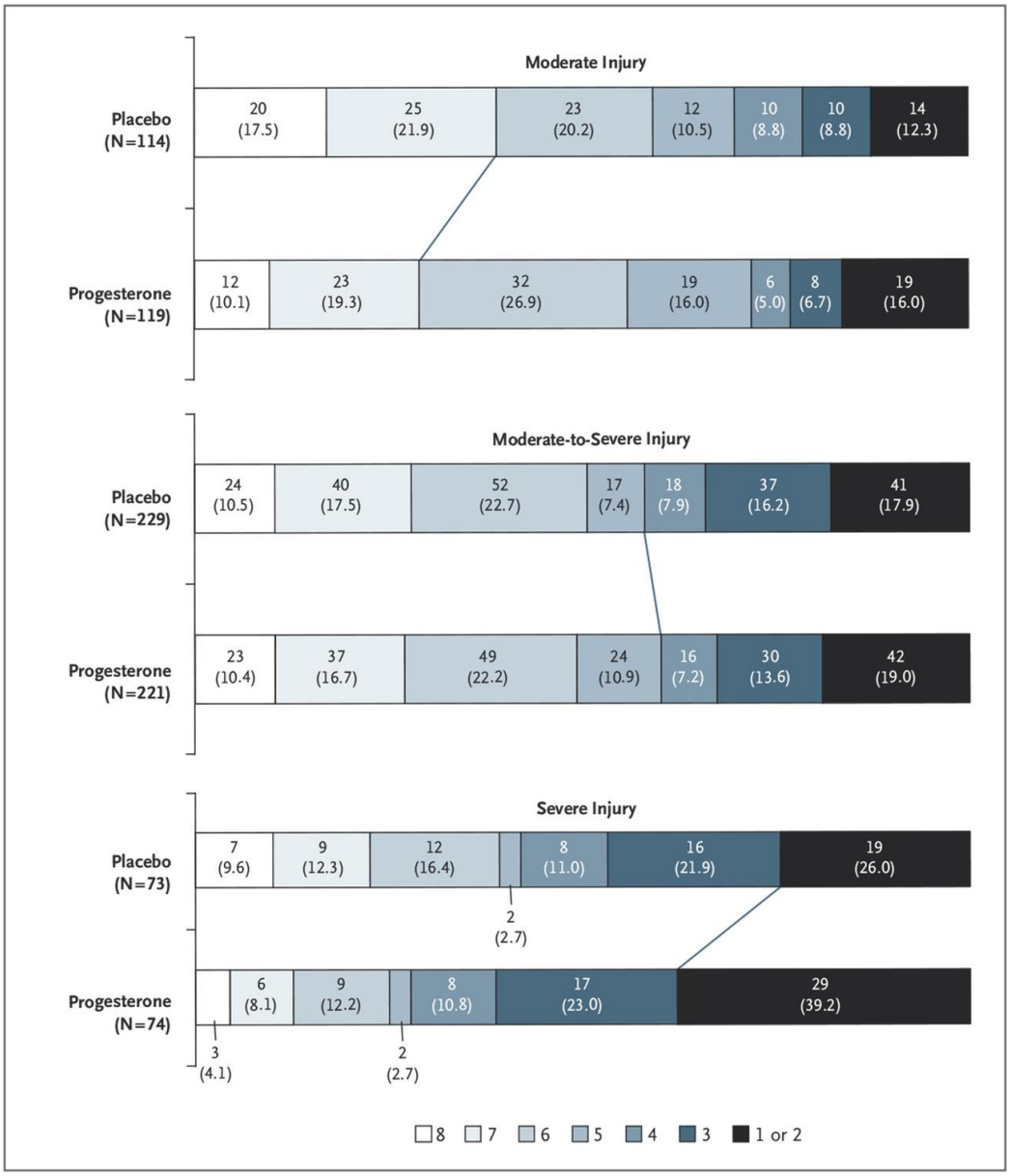

Figure 2. Stratified Distribution of the Extended Outcome Score (GOS-E), based on Initial Injury Severity (As Diagnosed by the Glasgow Coma Scale (GCS))[32].

Of the 881 patients randomized into the clinical trial, only 829 of them were evaluated at the follow-up to determine their 6-month outcome. As a result, only these patients were utilized (Figure 3).

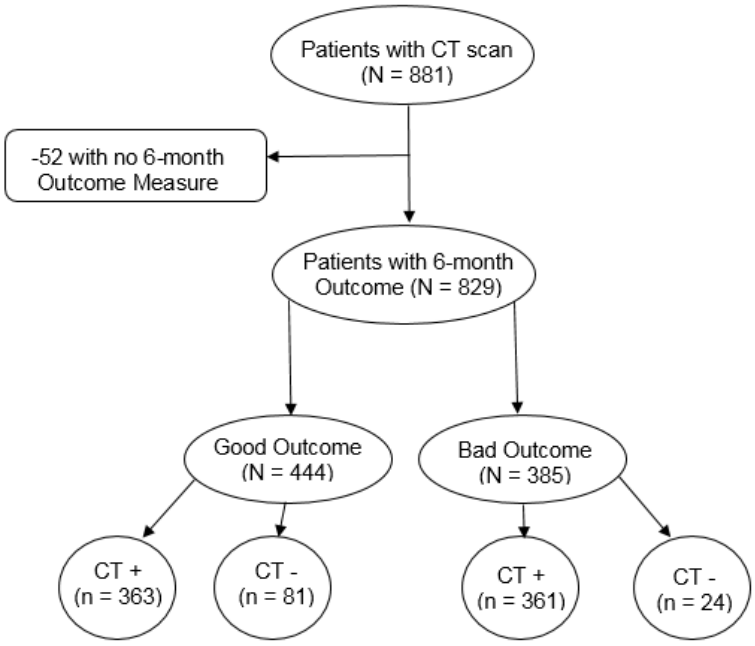

Figure 3. Study sample diagram of patients who had an initial CT scan and a 6-month outcome score stratified first by outcome score and then by CT scan.

Patient Characteristics and Measurements

Based on both an extensive search of the literature and a list of known predictors of TBI outcome, a list of patient characteristics and measurements were carefully compiled for analysis.[44-48] Demographic predictors included patient age, race, ethnicity, and gender. Medical history predictors included history of prior TBI, daily tobacco use, schizophrenia, social history issues, prescription drug abuse, nonprescription drug abuse, alcohol abuse, and depressed or suicidal gestures. Surgical procedures of interest included undergoing cranial surgery, extracranial surgery, a decompressive craniectomy, a cervical spinal stabilization, a percutaneous

endoscopic gastrostomy (PEG) tube installation, an installation of non-intraventricular intracranial pressure monitoring (ICP) monitor, a tracheostomy, and a ventriculostomy. Potential lab predictors included glucose level, hemoglobin count, platelet count, and international normalized ratio (INR). Other characteristics include whether or not the patient had a normal CT scan, time to the emergency department, total number of days in the intensive care unit (ICU), total number to days in the hospital, treatment arm, whether the patient is hypertensive or hypoxic, pupil response, mechanism of injury, intubation status, initial motor GCS score, initial verbal GCS score, initial eye GCS score, injury severity score (ISS), Rotterdam score, and discharge location.

A patient was deemed to be hypoxic if his or her pO_2 was less than 60 mmHg or O_2(sat) was less than 90 mmHg for 5 consecutive minutes. Hypertension was defined as having a systolic blood pressure greater than 90 beats per minute twice at least 5 minutes apart. Cranial surgery was defined as having underwent at least one of the following procedures: craniofacial surgery, decompressive craniectomy, ventriculostomy for cerebral spinal fluid drainage, minimal debridement for penetrating injuries, extensive debridement for penetrating injuries, or installation of a non-intraventricular ICP monitor such as a Camino or bolt monitor. An extracranial surgery is defined as having had at least any one of the following surgeries: maxillofacial, extremity fracture lower limb (internal fixation), extremity fracture lower limb (external fixation), extremity fracture upper limb (external fixation), extremity fracture upper limb (external fixation), fasciotomy, abdomen laparotomy, pelvic fracture (internal fixation), pelvic fracture (external fixation), cervical spinal stabilization, thoracotomy, tracheostomy, wound closure/graft, chest tube, or PEG tube installation. The total number of days in the hospital and ICU were derived from the daily checklists. The ISS is a composite measure of

three individual abbreviated injury scale (AIS) scores and can range from 3 to 75. AIS scores are calculated for each of seven different physiological locations (i.e., head, neck, face, chest, abdomen, extremity, and external (skin)) using the following scale: minor injury = 1, moderate injury = 2, serious injury = 3, severe injury = 4, critical injury = 5, unsurvivable injury = 6). The three highest local scores are first squared and then summed to get the ISS. It is worth noting that if one of the three highest AIS scores is a 6, the ISS value is automatically equal to 75. The higher the ISS, the more severe the injury.

Aims of Analysis

This thesis serves to accomplish the following aims:

1. Within the overall cohort of patients randomized into the clinical trial (N = 881), which patient characteristics are associated with CT scan?
2. Within the cohort of patients for whom a 6-month outcome score was obtained (N = 829), which patient characteristics can be used to predict a favorable outcome, as defined by the dichotomous version of GOS-E scores dependent on severity of injury?
3. Within the cohort of patients who exhibited a normal CT scan upon admission into the study (N = 105), is treatment (i.e., Progesterone versus Placebo) associated with a favorable outcome, as defined by the dichotomous GOS-E?
4. Within the normal CT cohort of patients (N = 105), what patient characteristics are associated with predicting a favorable outcome, as defined by the dichotomous GOS-E?

Statistical Analysis Plan – Descriptive Statistics and Univariate Statistical Analysis

As previously discussed, the primary outcome of interest is whether or not the patient exhibited functional recovery as determined by a binary version of the Extended Glasgow Outcome Scale at 6 months (Figure 2).

First, overall descriptive statistics for each of the individual predictors stratified by CT scan were generated. In addition, descriptive statistics were generated for each of the predictors stratified by the dichotomous GOS-E outcome. Tables of descriptive statistics were lastly created for the abnormal CT and normal CT cohorts of each of the individual predictors stratified by the dichotomous favorable/unfavorable outcome.

Univariate hypothesis testing was performed on each of the potential predictors and the respective outcome of interest for the overall cohort of patients stratified by CT scan and dichotomous outcome. Univariate hypothesis testing was additionally conducted on the cohort of patients with a normal CT scan stratified by outcome. For the nominal categorical predictors, χ^2 tests of independence and Fisher's exact test were conducted when appropriate. For the ordinal categorical predictors, the Cochran–Mantel–Haenszel (CMH) test was performed. Due to the relatively large sample size of the cohorts, independent t-tests were utilized to conduct hypothesis testing between the continuous variables and the outcome of interest. In these analyses, an equality of variance test was additionally performed to assess whether the pooled or Satterthwaite t-test should be utilized. Univariate odds ratios, along with their respective 95% Wald confidence intervals, were also generated using univariate logistic regression for each of the individual predictors in relation to the outcome of interest in the overall cohort (N = 829) and the normal CT cohort (N = 105).

Where applicable, contingency tables were collapsed to appropriately handle cells with sparse data and generate meaningful odds ratios. All statistical analyses of this dataset were performed in SAS version 9.4 statistical software developed by the SAS Institute (Cary, NC). We chose a significance level of $\alpha = 0.05$ for all portions of this univariate analysis. A p-value less than $\alpha = 0.05$ was therefore considered statistically significant.

Statistical Analysis Plan - Model Selection

This thesis presents three different methods of conducting multivariable logistic model selection. Before these procedures are discussed in detail, it is first necessary to introduce a few statistics that will be used in these processes. Deviance (D) measures the extent to which a current model deviates from the full/saturated model by comparing the likelihood functions. From asymptotic theory, the equation for deviance is as follows,

$$D = -2\{\log \hat{L}_c - \log \hat{L}_f\}$$

where $\hat{L}_c$ and $\hat{L}_f$ are the likelihood functions for the current model and saturated model, which contains all main effects predictors, respectively. A large deviance occurs when $\hat{L}_c$ is small relative to $\hat{L}_f$, indicative of the current model being a poor model. Likewise a small deviance value occurs when $\hat{L}_f$ and $\hat{L}_c$ are similar, indicating that the current model is an appropriate model. Additional statistics that will be utilized in model selection are the generalized coefficient of determination (R^2), the Akaike Information Criterion (AIC), and the Schwarz Criterion (SC). The generalized coefficient of determination is calculated by the following equation,

$$R^2 = 1 - \left(\frac{L(0)}{L(\hat{\beta})}\right)^{2/n}$$

where $L(0)$ is the likelihood of the intercept-only model, $L(\hat{\beta})$ is the likelihood of the current model, and n is the sample size. The AIC is defined as follows:

$$AIC = -2LogL + 2((k-1)+s)$$

where L is the likelihood of the model, k is the number of levels of the dependent variable and s is the number of predictors in the model. The SC is defined by the following:

$$SC = -2LogL + \big((k-1)+s\big)\log(\sum f_i)$$

where f_i's are the frequency values of the i^{th} observation, and L, k, and s are the likelihood, number of levels of the dependent variable, and the number of predictors in the model respectively. In model selection, the best or most parsimonious model is that model that exhibits the lowest AIC and SC while having the largest R^2.

The first model selection method that will be utilized is the automatic variable selection procedure. Three types of this procedure exist: forward, backward, and stepwise selection. In forward selection, variables are added to the model one at a time such that with each addition, the largest decrease in deviance occurs. Forward selection stops when the remaining variables do not significantly reduce the deviance by a pre-specified amount. In backward selection, often called backward elimination, the fully saturated model containing all of the variables is first implemented. As the selection process begins, each variable is excluded one at a time. If the removal of that variable significantly increases the deviance by a pre-specified amount (e.g., 2.71 ($X^2_{0.1,1}$) or 3.84 ($X^2_{0.05,1}$)), it is retained in the model, otherwise it is removed. This selection process ends when all variables remaining in the model increase the deviance by the pre-specified amount when individually dropped. In stepwise model selection, the process works similar to forward selection in that each variable is added to the model one at a time starting with the variable that gives the largest decrease in deviance upon its inclusion. However, once a new

variable is added to the model, the procedure checks to see whether any previously-included variable can be dropped from the model without causing a significant increase in the deviance. These automated approaches were utilized to create three separate logistic models predicting favorable outcome in the entire cohort of patients (N = 829). For these selection procedures, a strict α level of 0.05 ($\Delta D = 3.84$ ($X^2_{0.05,1}$)) was chosen.

The second method that will be utilized is a particular model selection procedure detailed by Collett (2003) that involves the manual or by-hand creation of the model.[49] The procedure consists of the following steps:

1. Univariate logistic models of the following form, $logit\ (p) = \beta_0 + \beta_j x_j$ for $j = 1, \ldots, k$) are individually fit for k predictors. These deviances are individually compared to the deviance from the null model, $logit\ (p) = \beta_0$. The variables that individually significantly reduce the deviance by a pre-specified amount (usually conservative significance level such as 10%). These variables are then fit together in a model (Model 1).
2. From Model 1, individual terms are dropped one by one. Only those variables that induce a significant change in the deviance are selected to remain in the model (Model 2).
3. Variables that were not selected on their own for inclusion into the initial model (i.e., Model 1), are added in to Model 2. Any variable that significantly reduces the deviance is added in to the model (Model 3).
4. A final evaluation is conducted to ensure that no term can be added to Model 3 to significantly reduce the deviance or deleted without significantly increasing the

deviance. The model that is developed at the end of this step is the final model (Model 4).

It is important to note that due to the large amount of potential predictors, not all of them were included in the initial step of this selection procedure. Only those predictors whose univariate association with the 6-month outcome was less than or equal to $\alpha = 0.30$ were selected for this process. It is also worth noting that while not performed in this analysis, interaction terms and higher order terms should be added to the model in Step 3 after ensuring that all first order terms have been appropriately included. This manual method was utilized to create an additional logistic model predicting favorable outcome in the entire cohort of patients (N = 829). It should be noted that a conservative α level of 0.10 was chosen for this manual method. Therefore a significant change in deviance was noted at a change in deviance of 2.71 ($X^2_{0.1,1}$).

A third approach, making use of the automated selection procedures, was also implemented. In this process, variables are divided into three domains based on their characteristics: the demographic/social history domain, the exam/lab/imaging domain, and the interventions/surgeries domain (Figure 4). Certain variables that were included in the univariate analysis were not included in model selection due to their clinical correlation to more relevant variables in the dataset. For example, since a Rotterdam score is assigned base on the CT scan results, we chose to remove Rotterdam from being selected during model selection. Other variables that were dropped include discharge location as CT scan results direct where patients are discharged and whether or not the patient underwent cranial or extracranial surgeries as the individual surgeries such as PEG tube installation were included instead.

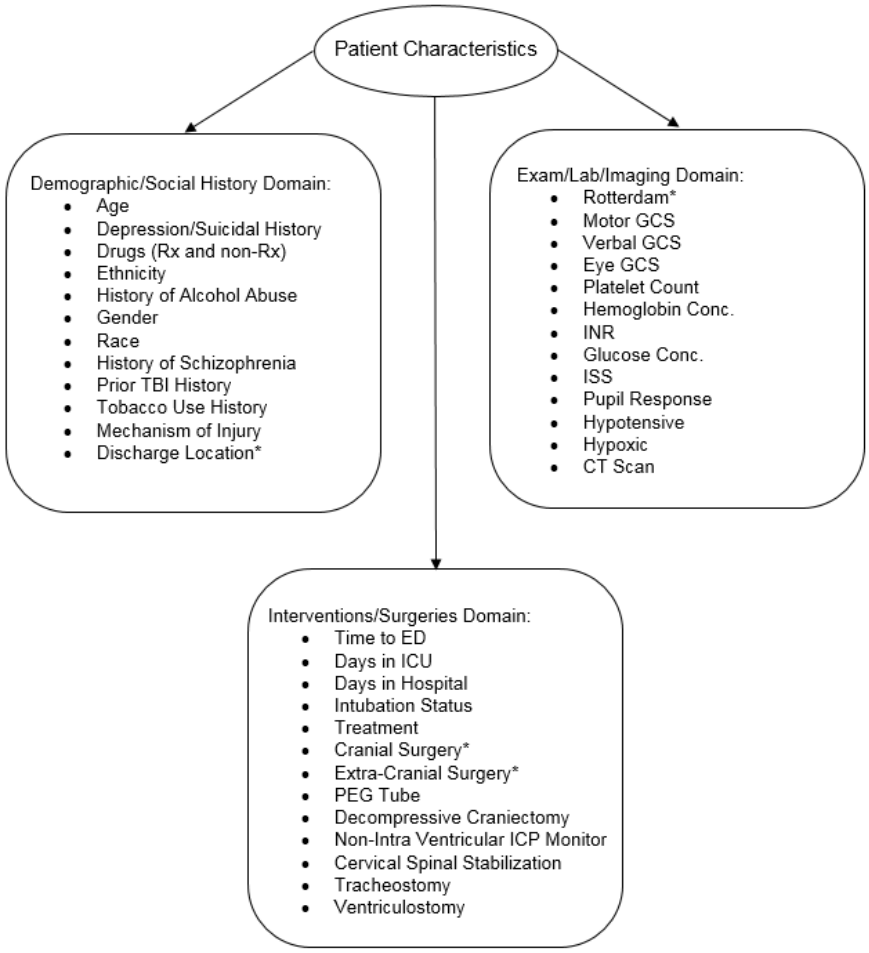

Figure 4. The 3 patient characteristic domains that were utilized for model selection.

Forward, backward, and stepwise automated selection procedures were performed on the demographic, exam/lab/imaging, and intervention domain to create three "initial" models per domain. Out of the nine initial models that were created (3 domains x 3 selection methods), any variable that was found in any of these final initial models was included for selection into the final domain model. Forward, backward, and stepwise selection were then implemented to generate three final models based on the domain approach. It is worth noting that for the "initial" domain models, a very conservative α level of 0.20 was chosen while the usual α level of 0.05

was selected for the final domain model selection. This domain approach was used to create logistic models for predicting favorable outcome in both the entire cohort of patients and in the cohort of patients with a normal CT scan.

A final model for the entire cohort of patients (N = 829) chosen by comparing the deviance, AIC, R^2, and SC of the seven models that were generated using the three different selection procedures (i.e., 3 from automated selection, 1 from Collet, and 3 from automated domain method). A similar process was utilized to choose a final model for the cohort of patients with a normal CT scan (N = 105).

Statistical Analysis Plan - Multivariable Statistical Analysis

After the two final models were selected, one for the overall cohort of patients and one for the cohort of patients with a normal CT scan, multivariable analysis was conducted on each model to generate adjusted odds ratios for the individual risk factors and their 95% Wald confidence intervals. Much like the marginal odds ratios that were previously obtained, these measure an association between the outcome of interest and a singular risk factor. However, these adjusted odds ratios account for the other risk factors in the model and therefore, give us a better understanding of the relationship between the patient characteristics and the outcome. The Hosmer-Lemeshow test additionally employed to assess goodness of fit for the two final models. This method arbitrarily groups the data into g groups of similar size and compares the total number of patients with a favorable 6-month outcome to the expected number of patients with a favorable 6-month outcome. Under the null hypothesis that the model is a significantly good fit, the Hosmer-Lemeshow statistic is distributed χ^2 with g – 1 degrees of freedom.

Results

Univariate Association between Patient Characteristics and CT scan (N = 881)

Table 5 details the univariate analysis of each of the patient characteristics with CT scan in the cohort of 881 patients randomized into the clinical trial. At an α level of 0.05, the following patient demographic and social history characteristics are significantly associated with CT scan: age, depression/suicidal status, history of prescription drug, tobacco and alcohol abuse, discharge location and mechanism of injury. Patient exam, lab and imaging characteristics associated with CT scan include initial glucose level, verbal GCS, eye GCS, and pupil response. Intervention and surgery patient characteristics that were associated with CT scan at an α level of 0.05 include intubation status, whether the patient had a cranial surgery, extracranial surgery, PEG tube installation, decompressive craniectomy, non intraventricular ICP monitor installation, tracheostomy, ventriculostomy, days in the ICU and hospital, and time to the emergency room.

Table 5. Patient characteristics stratified by CT scan. Univariate hypothesis testing was performed at an alpha level of 0.05.

		CT		
		Positive/Abnormal n (%) / mean (std)	Negative/Normal n (%) / mean (std)	P- Value
		n = 756	n = 125	
		Missing = 1		
Variable				
Gender				0.8649
	Male	557 (85.69)	93 (14.31)	
	Female	199 (86.15)	32 (13.85)	
Intubated				**0.0326***
	Yes	194 (90.23)	21 (9.77)	
	No	562 (84.38)	104 (15.62)	
Ethnicity				0.8211
	Hispanic/Latino	108 (86.40)	17 (13.60)	
	Not Hispanic/Latino	590 (85.63)	99 (14.37)	
	Missing	67		

Race				0.6625
	American Indian/Alaskan	6 (85.71)	1 (14.29)	
	Asian	38 (90.48)	4 (9.52)	
	Black/African American	118 (88.06)	16 (11.94)	
	Native Hawaiian/Pacific Islander	2 (66.67)	1 (33.33)	
	Caucasian	562 (85.15)	98 (14.85)	
	Other	30 (85.71)	5 (14.29)	
Mechanism of Injury				**0.0039*[a]**
	MVC	262 (81.37)	60 (18.63)	
	Pedestrian In MVC	106 (92.17)	9 (7.83)	
	Motorcycle/Moped	150 (88.76)	19 (11.24)	
	Bicycle	43 (93.48)	3 (6.52)	
	Fall < 3 feet	22 (81.48)	5 (18.52)	
	Fall ≥ 3 feet	101 (90.18)	11 (9.82)	
	Assault	41 (75.93)	13 (24.07)	
	Blast	2 (100.00)	0 (0.00)	
	Other	24 (85.71)	4 (14.29)	
	Missing	6		
Progesterone				0.9122
	Yes	379 (85.94)	62 (14.60)	
	No	377 (85.68)	63 (14.32)	
Discharge Location				**< 0.0001*[b]**
	Home	155 (68.28)	72 (31.72)	
	Hospice	6 (100.00)	0 (0.00)	
	Acute Facility	288 (92.60)	23 (7.40)	
	Sub-acute Facility	41 (89.13)	5 (10.87)	
	Long-term Acute	76 (97.44)	2 (2.56)	
	Skilled Nursing	40(86.96)	6 (13.04)	
	Assisted Living	0 (--)	0 (--)	
	Nursing Home Care	6 (85.71)	1 (14.29)	
	Morgue	118 (98.33)	2 (1.67)	
	Shelter	1 (50.00)	1 (50.00)	
	Other	16 (69.57)	7 (30.43)	
	Missing	15		
Cranial Surgery				**< 0.0001***
	Yes	438 (97.12)	13 (2.88)	
	No	318 (73.95)	112 (26.05)	
Extracranial Surgery				**< 0.0001***
	Yes	529 (89.97)	59 (10.03)	
	No	227 (77.47)	66 (22.53)	
Pupil Response				**0.0068***

	Unilateral	124 (94.66)	7 (5.34)	
	Bilateral	601 (84.17)	113 (15.83)	
	None	31 (86.11)	5 (13.89)	
PEG Tube				**< 0.0001***
	Yes	225 (96.98)	7 (3.02)	
	No	531 (81.82)	118 (18.18)	
Decompressive Craniectomy				**< 0.0001***
	Yes	150 (99.34)	1 (0.66)	
	No	606 (83.01)	124 (16.99)	
Depression /Suicidal				**0.0051***
	Yes	95 (77.24)	28 (22.76)	
	No	634 (86.85)	96 (13.15)	
	Missing	28		
Non-Prescription Drug Abuse				0.0715
	Yes	156 (82.11)	34 (17.89)	
	No	555 (87.26)	81 (12.74)	
	Missing	55		
Prescription Drug Abuse				**0.0003***
	Yes	25 (65.79)	13 (34.21)	
	No	636 (86.77)	97 (13.23)	
	Missing	110		
Alcohol Abuse				**0.0013***
	Yes	155 (78.28)	43 (21.72)	
	No	549 (87.56)	78 (12.44)	
	Missing	56		
Hypotension				1.0000
	Yes	13 (86.87)	2 (13.33)	
	No	743 (85.60)	123 (14.20)	
Hypoxia				0.6408
	Yes	8 (80.00)	2 (20.00)	
	No	748 (85.88)	123 (14.12)	
Non-intraventricular ICP monitor (Camino, bolt)				**< 0.0001***
	Yes	13 (86.87)	2 (13.33)	
	No	743 (85.80)	123 (14.20)	
Schizophrenia				0.4915
	Yes	16 (94.12)	1 (5.88)	
	No	716 (85.94)	121 (14.66)	
	Missing	27		
Social History				0.0831
	Yes	333 (83.46)	66 (16.54)	

	No	416 (87.58)	59 (12.42)	
	Missing	7		
Spinal Stabilization / Cervical				0.7056
	Yes	11 (84.62)	2 (15.38)	
	No	745 (85.83)	123 (14.17)	
Prior TBI				0.7190
	Yes	74 (87.06)	11 (12.94)	
	No	667 (85.62)	112 (14.38)	
	Missing	17		
Tobacco				**0.0295***
	Yes	240 (82.19)	52 (17.81)	
	No	465 (85.83)	65 (12.26)	
	Missing	59		
Tracheostomy				**< 0.0001***
	Yes	257 (97.35)	7 (2.65)	
	No	499 (80.88)	118 (19.12)	
Ventriculostomy				**< 0.0001***
	Yes	251 (98.05)	5 (1.95)	
	No	505 (80.80)	120 (19.20)	
eye GCS				**0.0123***
	1	408 (89.47)	48(10.53)	
	2	104 (78.20)	29 (21.80)	
	3	96 (87.27)	14 (12.73)	
	4	148 (81.32)	34 (18.68)	
verbal GCS				**0.0111***
	1	397 (88.03)	54 (11.97)	
	2	219 (86.56)	34 (13.44)	
	3	79 (77.45)	23 (22.55)	
	4	54 (81.82)	12 (18.18)	
	5	7 (77.78)	2 (22.22)	
motor GCS				0.2197
	1	15 (83.33)	3 (16.67)	
	2	60 (88.24)	8 (11.76)	
	3	94 (87.85)	13 (12.15)	
	4	248 (86.41)	39 (13.59)	
	5	321 (85.60)	54 (14.40)	
	6	18 (69.23)	8 (30.77)	
ISS		26.63 (11.24)	14.85 (9.90)	**< 0.0001***
Days in ICU		11.81 (8.35	4.88 (5.23)	**< 0.0001***
Total Days in Hospital		16.45 (9.43)	8.67 (7.24)	**< 0.0001***

Age (in years)	39.69 (17.85)	36.37 (15.40)	**0.0302***
Glucose (mg/dL)	153.61 (50.21)	137.38 (43.04)	**0.0003***
Hemoglobin (g/dL)	13.58 (1.87)	13.70 (1.84)	0.5220
INR	1.14 (0.47)	1.12 (0.35)	0.6595
Time to Emergency Department (min)	52.34 (27.11)	62.06 (36.42)	**0.0069***
Platelets (10^3/mm^3)	246.45 (9.43)	249.00 (71.47)	0.7157
a = mechanism of injury was collapsed to compare MVC to other injuries, b = discharge location was collapsed to compare Home/Shelter vs. Acute/Sub-acute/Long-term Acute/Skilled Nursing/Assisted Living/Nursing Home Care vs. Morgue/Other/Hospice, * = significant at α = 0.05			

Predicting 6-month Outcome in Entire Cohort (N = 829)

Table 6 details the univariate analysis of each of the patient characteristics with the dichotomized GOS-E outcome in the 829 patients whose 6-month outcome. At an α level of 0.05, the following patient demographic and social history characteristics are significantly associated with dichotomized GOS-E outcome: age, race, and discharge location. Patient exam, lab and imaging characteristics associated with 6-month outcome include Rotterdam score, initial hemoglobin level, ISS, verbal GCS, eye GCS, and pupil response. Intervention and surgery patient characteristics that were associated with 6-month dichotomized GOS-E outcome at an α level of 0.05 include whether the patient had a cranial surgery, decompressive craniectomy, non intraventricular ICP monitor installation, cervical spinal stabilization, tracheostomy, ventriculostomy, days in the ICU and time to the emergency room.

Table 6. Patient characteristics (n = 829) stratified by dichotomized outcome for all patients randomized into the ProTECT III clinical trial. Univariate hypothesis testing was performed at an alpha level of 0.05.

		Favorable Outcome		OR (CI_{95})	P-Value
		Yes n (%) / mean (std)	No n (%) / mean (std)		
		n = 444	n = 385		
		Missing = 52			
Variable					
Gender				1.158 (0.852, 1.574)	0.3491
	Male	330 (54.55)	275 (45.45)		
	Female^	114 (50.89)	110 (49.11)		
Intubated				1.337 (0.973, 1.839)	0.0732
	Yes	122 (58.94)	85 (41.06)		

	No^	322 (51.77)	300 (48.23)		
Ethnicity				1.300 (0.875, 1.930)	0.1930
	Hispanic/Latino	71 (59.17)	49 (40.83)		
	Not Hispanic/Latino^	340 (52.71)	305 (47.29)		
	Missing	64			
Race					0.3194[a]
	Caucasian	343 (54.53)	286 (45.47)	1.176 (0.855, 1.617)[a]	
	American Indian/Alaskan*	4 (57.14)	3 (42.86)		
	Asian^	14 (37.84)	23 (62.16)		
	Black/African American^	60 (49.18)	62 (50.82)		
	Native Hawaiian/Pacific Islander^	2 (66.67)	1 (33.33)		
	Other^	21 (67.74)	10 (32.26)		
Mechanism of Injury				1.942 (1.452, 2.097)[b]	**< 0.0001*[b]**
	MVC	194 (63.82)	110 (36.18)		
	Pedestrian In MVC^	39 (36.11)	69 (63.89)		
	Motorcycle/Moped^	88 (53.66)	76 (46.34)		
	Bicycle^	25 (58.14)	18 (41.86)		
	Fall < 3 feet^	8 (36.36)	14 (63.64)		
	Fall ≥ 3 feet^	49 (44.55)	61 (55.45)		
	Assault^	20 (44.44)	25 (55.56)		
	Blast^	2 (100.00)	0 (0.00)		
	Other^	16 (64.00)	9 (36.00)		
	Missing	6			
Progesterone				0.853 (0.649, 1.121)	0.2536
	Yes	213 (55.57)	200 (48.43)		
	No^	231 (55.53)	185 (44.47)		
Discharge Location					**< 0.0001*[c]**
	Home	148 (71.15)	60 (28.85)	36.896 (17.650, 77.126)[c]	
	Shelter	1 (50.00)	1 (50.00)		
	Acute Facility	201 (66.56)	101 (33.44)	22.979 (11.421, 46.233)[c]	
	Sub-acute Facility	30 (66.67)	15 (33.33)		
	Long-term Acute	35 (45.45)	42 (54.55)		
	Skilled Nursing	20 (45.45)	24 (54.55)		
	Assisted Living	0 (--)	0 (--)		
	Nursing Home Care	0 (0.00)	6 (100.00)		
	Morgue^	0 (0.00)	120 (100.00)		
	Hospice^	1 (16.67)	5 (83.33)		
	Other^	8 (42.11)	11 (57.89)		
Cranial Surgery				0.512 (0.388, 0.676)	**< 0.0001***

	Yes	200 (45.77)	237 (54.23)		
	No^	244 (62.24)	148 (37.76)		
Extracranial Surgery				1.207 (0.901, 1.617)	0.2066
	Yes	310 (55.06)	253 (44.94)		
	No^	134 (50.38)	132 (49.62)		
Pupil Response					**0.0426***
	Unilateral	60 (48.00)	65 (52.00)	1.562 (0.723, 3.375)	
	Bilateral	371 (55.46)	298 (44.54)	2.107 (1.044, 4.253)	
	None^	13 (37.14)	22 (62.86)		
PEG Tube				0.745 (0.549, 1.103)	0.0597
	Yes	109 (48.23)	117 (51.77)		
	No^	335 (55.56)	268 (44.44)		
Decompressive Craniectomy				0.399 (0.276, 0.578)	**< 0.0001***
	Yes	52 (35.14)	96 (64.86)		
	No^	392 (57.56)	289 (42.44)		
Depression /Suicidal				1.134 (0.762, 1.688)	0.5356
	Yes	65 (56.62)	50 (43.48)		
	No^	368 (53.41)	321 (46.59)		
	Missing	25			
Non-Prescription Drug Abuse				1.123 (0.803, 1.569)	0.4971
	Yes	100 (55.56)	80 (44.44)		
	No^	315 (52.86)	283 (47.32)		
	Missing	51			
Prescription Drug Abuse				1.324 (0.666, 2.631)	0.4215
	Yes	22 (61.11)	14 (38.89)		
	No^	375 (54.27)	316 (45.73)		
	Missing	102			
Alcohol Abuse				1.618 (1.149, 2.280)	**0.0057***
	Yes	115 (63.54)	66 (36.46)		
	No^	309 (51.85)	287 (48.15)		
	Missing	52			
Hypotension				0.754 (0.271, 2.099)	0.5891
	Yes	7 (46.67)	8 (53.33)		
	No^	437 (53.69)	377 (46.31)		
Hypoxia				1.744 (0.433, 7.021)	0.4279
	Yes	6 (66.67)	3 (33.33)		
	No^	438 (53.41)	382 (46.59)		
Non-intraventricular ICP monitor (Camino, bolt)				0.612 (0.432, 0.868)	**0.0056***
	Yes	69 (43.67)	89 (56.33)		

	No^	375 (55.89)	296 (44.11)		
Schizophrenia				0.475 (0.158, 1.429)	0.1756
	Yes	5 (35.71)	9 (64.29)		
	No^	426 (53.92)	364 (46.08)		
	Missing	25			
Social History				1.307 (0.991, 1.723)	0.0574
	Yes	214 (57.53)	158 (42.47)		
	No^	229 (50.89)	221 (49.11)		
	Missing	7			
Cervical Spinal Stabilization				> 999.999 (0, ∞)	**0.0012***
	Yes	12 (100.00)	0 (0.00)		
	No^	432 (52.88)	385 (47.12)		
Prior TBI				1.374 (0.862, 2.192)	0.1807
	Yes	50 (60.98)	32 (39.02)		
	No^	390 (53.21)	343 (46.79)		
	Missing	13			
Tobacco				1.016 (0.823, 1.486)	0.5026
	Yes	154 (55.80)	122 (44.20)		
	No^	267 (53.29)	234 (46.71)		
	Missing	52			
Tracheostomy				0.743 (0.553, 0.998)	**0.0481***
	Yes	124 (48.44)	132 (51.56)		
	No^	320 (55.85)	253 (44.15)		
Ventriculostomy				0.590 (0.438, 0.796)	**0.0005***
	Yes	112 (44.44)	140 (55.56)		
	No^	332 (57.54)	245 (42.46)		
ISS		23.26 (11.68)	27.63 (11.30) [	0.968 (0.956, 0.980)	**< 0.0001***
Days in ICU		10.57 (7.89)	11.74 (8.63)	0.983 (0.967, 0.999)	**0.0412***
Total Days in Hospital		15.76 (8.98)	15.59 (9.95)	1.002 (0.988, 1.017)	0.7955
Age (in years)		35.08 (15.31)	44.29 (19.12)	0.97 (0.962, 0.978)	**< 0.0001***
Glucose (mg/dL)		148.91 (44.77)	155.77 (55.06)	0.997 (0.994, 1.000)	0.0549
Hemoglobin (g/dL)		13.80 (1.86)	13.38 (1.85)	1.131 (1.048, 1.219)	**0.0013***
INR		1.14 (0.60)	1.13 (0.26)	1.025 (0.751, 1.397)	0.8718
Time to Emergency Department (min)		55.84 (27.99)	50.73 (27.30)	1.007 (1.002, 1.012)	**0.0083***
Platelets (10^3/mm^3)		245.15 (71.68)	248.68 (71.10)	0.999 (0.997, 1.001)	0.4818
eye GCS				0.705 (0.536, 0.927)[d]	**0.0123***
	1	252 (57.67)	185 (42.33)		
	2^	66 (55.00)	54 (45.00)		
	3^	51 (48.57)	54 (51.43)		

	4^	75 (44.91)	92 (55.09)		
verbal GCS				0.673 (0.512, 0.886)[d]	**0.0047***
	1	249 (58.31)	178 (41.69)		
	2^	127 (53.14)	112 (46.86)		
	3^	41 (42.71)	55 (57.29)		
	4^	22 (37.29)	37 (62.71)		
	5^	5 (62.50)	3 (37.50)		
motor GCS				0.848 (0.644, 1.115)[e]	0.2373
	1	13 (81.25)	3 (18.75)		
	2	36 (59.02)	25 (40.98)		
	3	56 (53.85_	48 (46.15)		
	4^	145 (53.70)	125 (46.30)		
	5^	182 (51.27)	173 (48.73)		
	6^	12 (52.17)	11 (47.83)		
Rotterdam					**< 0.0001***
	1^	8 (61.54)	5 (38.46)		
	2	189 (66.32)	96 (33.68)	1.230 (0.392, 3.863)	
	3	203 (53.85)	174 (46.15)	0.729 (0.234, 2.270)	
	4	26 (34.67)	49 (65.33)	0.332 (0.098, 1.117)	
	5	16 (23.88)	51 (76.12)	0.196 (0.056, 0.685)	
	6	2 (16.67)	10 (83.33)	0.125.019, 0.823)	
^ = reference group, a = race was collapsed to compare whites to others, b = mechanism of injury was collapsed to compare MVC to other injuries, c = discharge location was collapsed to compare Home/Shelter vs. Acute/Sub-acute/Long-term Acute/Skilled Nursing/Assisted Living/Nursing Home Care vs. Morgue/Other/Hospice, d = verbal and motor GCS were collapsed into 1 vs > 1, e = motor GCS was collapsed into < 4 vs. > 4, * = significant at α = 0.05					

From the automated forward, backwards, and stepwise selection of the variables, the list of variables that were significant at an α level of 0.05 in each of the models is detailed in Table 7. In forward selection, verbal GCS, CT scan, age, ISS, and whether the patient underwent non-intraventricular ICP monitor installation, cervical spinal stabilization, a prior TBI, and a ventriculostomy were deemed to be significant. The model selected from backwards selection included verbal GCS, CT scan, age, ISS, number of days in ICU and hospital, and whether the patient underwent a decompressive craniectomy. Stepwise selection lead to a super restrictive model containing only verbal GCS and age. The list of variables significant in Collett's deviance model are also listed in Table 7. They included age, ISS, ethnicity, mechanism of injury, initial

glucose and hemoglobin levels, eye GCS, history of alcohol abuse, schizophrenia, and a prior TBI, and whether the patient underwent non-intraventricular ICP monitor installation, cervical spinal stabilization, or a ventriculostomy.

Table 7. Patient characteristics selected into the models for the entire cohort of patients (n = 829) based on automated (forward, backward, stepwise) selection, Collett's deviance selection, and the Domain automated selection.

	Automated - Forward	Automated - Backward	Automated - Stepwise	Collett / Deviance	Domain - Forward	Domain - Backward	Domain - Stepwise	Total
Variable								
Verbal GCS	X	X			X			3
CT Scan	X	X	X		X	X	X	6
Age	X	X	X	X	X	X	X	7
ISS	X	X		X	X	X	X	6
Non-Intraventricular ICP Monitor	X			X	X			3
Cervical Spinal Stabilization	X			X	X			3
Prior TBI	X			X				2
Ventriculostomy	X			X				2
PEG Tube		X						1
Days in ICU		X				X		2
Days in Hospital		X				X		2
Decompressive Craniectomy		X			X	X		3
Ethnicity				X				1
Mechanism of Injury				X				1
Alcohol Abuse				X				1
Schizophrenia				X				1
Glucose				X				1
Hemoglobin				X				1
Eye GCS				X				1
Intubation						X		1

The results of the initial domain automated procedures are detailed in Table 8. As a result, the variables that were chosen for consideration into the final domain model selection included age, mechanism of injury, history of alcohol abuse, prescription drug abuse, and prior TBI, eye, motor and verbal GCS, CT scan, hemoglobin and platelet concentration, ISS, whether

or not the patient was hypoxic, pupil response, time to the emergency department, days in the ICU and hospital, intubation status, and whether or not the patient underwent a decompressive craniectomy, non-intraventricular ICP monitor installation, cervical spinal stabilization, or a ventriculostomy.

Table 8. Patient Characteristics selected into models based on automated model selection of domains for the entire cohort of patients (N = 829), F = forward selection, B = backward selection, SW = stepwise selection.

	Demographics / Social History	Exam / Lab / Imaging	Interventions / Surgeries
Variable			
Age	F/B/SW		
Prescription Drug Abuse	F/B/SW		
Alcohol Abuse	F/B/SW		
Mechanism of Injury	F/B/SW		
Prior TBI	F/B/SW		
Depression / Suicidal Thoughts			
Non-Prescription Drug Abuse			
Race			
Eye GCS		F/B/SW	
Verbal GCS		F/B	
Motor GCS		F	
CT Scan		F/B/SW	
Hemoglobin		F/B/SW	
Platelets		F/B	
ISS		F/B/SW	
Hypoxia		F	
Pupil Response		F/B	
Glucose			
INR			
Decompressive Craniectomy			F/B/SW
Intubation Status			F/B/SW
Non-Intraventricular ICP Monitor			F/B/SW
Cervical Spinal Stabilization			F/B/SW
Time to ED			F/B/SW
Ventriculostomy			F/B/SW
Days in ICU			B
Total Days in Hospital			B

Table 7 details the results of the three final domain models that were generated using forward, backward, and stepwise selection. Forward selection chose verbal GCS, CT scan, age, ISS, non-intraventricular ICP monitor, cervical spinal stabilization, and decompressive craniectomy into the model. Backward selection selected CT scan, age, ISS, number of days in ICU and hospital, decompressive craniectomy, and intubation status into the final model while stepwise selection chose only age, CT scan, and ISS. Based on these results, each of the seven models were analyzed for determining a final parsimonious model for this cohort of normal CT patients. The results of this final selection procedure based on AIC, SC, and R^2 are detailed in Table 9.

Table 9. Model Statistics for assessing the final model that best predicts patient outcome in the overall cohort of patients. AIC = Akaike Information Criterion, SC = Schwarz Criterion, R^2 = generalized coefficient of determination.

Model	AIC	SC	R^2
Automated - Forward	795.450	848.988	0.1581
Automated - Backward	805.996	859.534	0.1441
Automated - Stepwise	830.672	844.061	0.0872
Collett / Deviance	783.207	854.082	0.1534
Domain - Forward	796.571	845.647	0.1540
Domain - Backward	807.667	843.359	0.1311
Domain - Stepwise	819.398	837.244	0.1039

Since we are interested in the model with best combination of the lowest AIC, lowest SC, and highest R^2, the model that was selected via automated forward selection was chosen as the best model of the data and takes the following form:

$$\begin{aligned} logit\,(p_i) = {} & -0.339 - 0.910verbalGCS_2 - 1.071verbalGCS_3 - 0.684verbalGCS_4 \\ & - 0.961verbalGCS_5 - 0.961CTpos - 0.028age - 0.022ISS - 0.630ICP \\ & + 15.208spinal\_stab + 0.590prior\_tbi - 0.385ventriculostomy \end{aligned} \quad \text{(Model 1)}$$

The beta estimates standard, adjusted odds ratios, their 95% confidence intervals, and p-values are detailed in Table 10. As compared to a verbal GCS score of 1, the odds of a favorable GOS-E outcome was found to not be statistically different in patients with a GCS of 2 (OR = 0.712, CI_{95}: [0.480, 1.056], p-value = 0.0912) and a GCS of 5 (OR = 0.505, CI_{95}: [0.072, 3.557], p-value = 0.4925) but was found to be statistically significant in patients with a score of 3 (OR = 0.403, CI_{95}: [0.224, 0.726], p-value = 0.0025) and 4 (OR = 0.343, CI_{95}: [0.170, 0.689], p-value = 0.0027). Additional patient characteristics that were found to be statistically significant in predicting a favorable GOS-E patient outcome include patient age (OR = 0.973 , CI_{95}: [0.963, 0.982], p-value = < 0.0001), ISS (OR = 0.978, CI_{95}: [0.963, 0.994], p-value = 0.0067), whether or not they underwent a non-intraventricular ICP monitor installation (OR = 0.532, CI_{95}: [0.341, 0.831], p-value = 0.0055), prior TBI (OR = 1.803, CI_{95}: [1.017, 3.199], p-value = 0.0437), or ventriculostomy (OR = 0.680, CI_{95}: [0.463, 0.998], p-value = 0.0491). While not statistically significant, whether or not the patient underwent a cervical spinal stabilization procedure was included in the model (p-value = 0.9800).

Finally a Hosmer-Lemeshow goodness of fit test of this model allows us to conclude that it fits the data well (χ^2 = 4.3936, df = 8, p-value = 0.8200). This suggests a good fit exists between the observed and fitted values from the logistic model.

Table 10. Final Multivariable model that best predicts patient outcome for the overall cohort of patients upon inclusion into the ProTECT III clinical trial.

Variable	Level	Beta	SE	Adjusted OR (CI_{95})	p-value
Verbal GCS					
	2 vs 1	-0.3394	0.2009	0.712 (0.480, 1.056)	0.0912
	3 vs 1	-0.9096	0.3004	0.403 (0.224, 0.726)	0.0025
	4 vs 1	-1.0708	0.3565	0.343 (0.170, 0.689)	0.0027
	5 vs 1	-0.6837	0.9962	0.505 (0.072, 3.557)	0.4925
CT scan	Positive vs Negative	-0.9611	0.3208	0.382 (0.204, 0.717)	0.0027
Age		-0.0278	0.00489	0.973 (0.963, 0.982)	< 0.0001
ISS		-0.0222	0.00818	0.978 (0.963, 0.994)	0.0067
Non-Intraventricular ICP monitor		-0.6303	0.2272	0.532 (0.341, 0.831)	0.0055
Cervical Spinal Stabilization		15.2084	607	> 999.999 (0, ∞)	0.9800
Prior TBI		0.5897	0.2924	1.803 (1.017, 3.199)	0.0437
Ventriculostomy		-0.3853	0.1958	0.680 (0.463, 0.998)	0.0491

Predicting 6-month Outcome in patients with normal CT scan (N = 105)

In Table 11, the univariate analysis of patient characteristics with the dichotomized GOS-E favorable outcome in the 829 patients whose 6-month outcome is detailed. Within this cohort of normal CT patients, the only characteristics significantly associated with the 6-month outcome are discharge location, history of non-prescription drug abuse, and initial verbal GCS score. With respect to discharge location, the odds of a favorable GOS-E outcome was 16 (1.731, 147.892) times higher for patients who were discharged home compared to the morgue or hospice and 39 (3.682, 434.523) times higher for patients discharged to the acute, sub-acute, long-term acute, skilled nursing, assisted living, nursing home care compared to the morgue and hospice. In addition, the odds of a favorable outcome among patients with a history of non-prescription drug abuse is 0.273 (0.102, 0.729) times the odds of favorable GOS-E outcome among those without a history of abuse. From this table, we can see that progesterone treatment is not associated with the 6-month dichotomized GOS-E outcome (OR: 0.571 (0.227, 1.437)).

Table 11. Patient characteristics stratified by Dichotomized GOS-E Favorable Outcome for patients with a normal CT upon admission into the ProTECT III clinical trial. Univariate hypothesis testing and confidence interval generation was performed at an alpha level of 0.05.

		Favorable Outcome		OR (CI_{95})	P-value
		Yes n (%) / mean(std)	No n (%) / mean (std)		
		n = 81	n = 24		
		Missing = 20			
Variable					
Progesterone				0.571 (0.227, 1.437)	0.2315
	Yes	36 (72.00)	14 (28.00)		
	No^	45 (81.82)	10 (18.18)		
Gender				1.261 (0.475, 3.348)	0.6413
	Male	58 (78.38)	16 (21.62)		
	Female^	23 (74.19)	8 (25.81)		
Intubated				0.956 (0.280, 3.257)	1.0000
	Yes	13 (76.47)	4 (23.53)		
	No^	68 (77.27)	20 (22.73)		
Ethnicity				0.829 (0.237, 2.907)	1.0000
	Hispanic/Latino	11 (73.33)	4 (26.67)		
	Not Hispanic/Latino^	63 (76.83)	19 (23.17)		
	Missing	8			
Race				2.301 (0.740, 5.575)[a]	0.1641[a]
	Caucasian	65 (80.25)	16 (19.75)		
	American Indian/Alaskan^	1 (100.00)	0 (0.00)		
	Asian^	3 (75.00)	1 (25.00)		
	Black/African American^	9 (64.29)	5 (35.71)		
	Native Hawaiian/Pacific Islander^	1 (100.00)	0 (0.00)		
	Other^	2 (50.00)	2 (50.00)		
Mechanism of Injury				1.472 (0.585, 3.702)[b]	0.4101[b]
	MVC	41 (80.39)	10 (19.61)		
	Pedestrian In MVC^	6 (75.00)	2 (25.00)		
	Motorcycle/Moped^	12 (66.67)	6 (33.33)		
	Bicycle^	3 (100.00)	0 (0.00)		
	Fall < 3 feet^	2 (66.67)	1 (33.33)		
	Fall ≥ 3 feet^	7 (77.78)	2 (22.22)		
	Assault^	5 (62.50)	3 (37.50)		
	Blast^	0 (--)	0 (--)		
	Other^	4 (100.00)	0 (0.00)		
	Missing	1			
Progesterone				0.571 (0.227, 1.437)	0.2315

	Yes	36 (72.00)	14 (28.00)		
	No^	45 (81.82)	10 (18.18)		
Discharge Location					**0.0013***
	Home	47 (75.81)	15 (24.19)	16 (1.731, 147.892)[c]	
	Shelter	1 (100.00)	0 (0.00)		
	Acute Facility	22 (95.65)	1 (4.35)	39.999 (3.682, 434.523)[c]	
	Sub-acute Facility	5 (100.00)	0 (0.00)		
	Long-term Acute	1 (50.00)	1 (50.00)		
	Skilled Nursing	4 (80.00)	1 (20.00)		
	Assisted Living	0 (--)	0 (--)		
	Nursing Home Care	0 (0.00)	1 (100.00)		
	Morgue^	0 (0.00)	2 (100.00)		
	Hospice^	0 (--)	0 (--)		
	Other^	1 (25.00)	3 (75.00)		
Cranial Surgery				0.986 (0.248, 3.915)	1.0000
	Yes	10 (76.92)	3 (23.08)		
	No^	71 (77.17)	21 (22.83)		
Extracranial Surgery				1.665 (0.662, 4.185)	0.2760
	Yes	44 (81.48)	10 (18.52)		
	No^	37 (72.55)	14 (27.45)		
Pupil Response					0.3688
	Unilateral	4 (66.67)	2 (33.33)	1.333 (0.113, 15.704)	
	Bilateral	74 (78.72)	20 (21.28)	2.467 (0.385, 15.784)	
	None^	3 (60.00)	2 (40.00)		
PEG Tube				1.840 (0.211, 16.082)	1.0000
	Yes	6 (85.71)	1 (14.29)		
	No^	75 (76.53)	23 (23.47)		
Decompressive Craniectomy				NA	0.2286
	Yes	0 (0.00)	1 (100.00)		
	No^	81 (77.88)	23 (22.12)		
Depression /Suicidal				0.607 (0.215, 1.712)	0.3426
	Yes	16 (69.57)	7 (30.43)		
	No^	64 (79.01)	17 (20.99)		
	Missing	1			
Non-Prescription Drug Abuse				0.273 (0.102, 0.729)	**0.0075***
	Yes	17 (58.62)	12 (41.38)		
	No^	57 (83.82)	11 (16.18)		
	Missing	8			
Prescription Drug Abuse				2.921 (0.352, 24.228)	0.4495

	Yes	11 (91.67)	1 (8.33)		
	No^	64 (79.01)	17 (20.99)		
	Missing	12			
Alcohol Abuse				0.734 (0.280, 1.922)	0.5278
	Yes	25 (73.53)	9 (26.47)		
	No^	53 (79.10)	14 (20.90)		
	Missing	4			
Hypotension				0.287 (0.017, 4.777)	0.4066
	Yes	1 (50.00)	1 (50.00)		
	No^	80 (77.67)	23 (22.33)		
Hypoxia				NA	1.0000
	Yes	2 (100.00)	0 (0.00)		
	No^	79 (76.70)	24 (23.30)		
Non-intraventricular ICP monitor (Camino, bolt)				0.571 (0.098, 3.329)	0.6179
	Yes	4 (66.67)	2 (33.33)		
	No^	77 (77.78)	22 (22.22)		
Schizophrenia				NA	1.0000
	Yes	1 (100.0)	0 (0.00)		
	No^	77 (76.24)	24 (23.76)		
	Missing	3			
Social History				0.697 (0.277, 1.750)	0.4410
	Yes	40 (74.07)	14 (25.93)		
	No^	41 (80.39)	10 (19.61)		
Cervical Spinal Stabilization				NA	1.0000
	Yes	2 (100.00)	0 (0.00)		
	No^	79 (76.70)	24 (23.30)		
Prior TBI				1.151 (0.227, 5.836)	1.0000
	Yes	8 (80.00)	2 (20.00)		
	No^	73 (77.66)	21 (22.34)		
	Missing	1			
Tobacco				0.583 (0.231, 1.469)	0.2498
	Yes	31 (70.45)	13 (29.55)		
	No^	45 (80.36)	11 (19.64)		
	Missing	5			
Tracheostomy				1.840 (0.211, 16.082)	1.0000
	Yes	6 (85.71)	1 (14.29)		
	No^	75 (76.53)	23 (23.47)		
Ventriculostomy				1.195 (0.127, 11.226)	1.0000
	Yes	4 (80.00)	1 (20.00)		
	No^	77 (77.00)	23 (23.00)		

ISS		15.19 (10.12)	13.96 (8.35)	1.014 (0.966, 1.064)	0.5895
Days in ICU		5.57 (5.55)	4.46 (5.44)	1.044 (0.947, 1.150)	0.3898
Total Days in Hospital		9.75 (7.43)	8.85 (7.65)	1.015 (0.952, 1.082)	0.6487
Age (in years)		35.93 (15.39)	36.46 (16.08)	0.998 (0.969, 1.027)	0.8831
Glucose (mg/dL)		144.68 (46.88)	128.65 (34.37) [	1.009 (0.997, 1.022)	0.1314
Hemoglobin (g/dL)		13.79 (1.93)	13.36 (1.71)	1.125 (0.888, 1.426)	0.3304
INR		1.12 (0.42)	1.14 (0.14)	0.850 (02.69, 2.683)	0.6635
Time to Emergency Department (min)		58.90 (28.61)	59.08 (34.86)	1.000 (0.985, 1.015)	0.9793
Platelets ($10^3/mm^3$)		251.41 (69.25)	240.08 (70.64	1.002 (0.996, 1.009)	0.4871
eye GCS				0.473 (0.187, 1.194)[d]	0.1090
	1	36 (85.71)	6 (14.29)		
	2^	19 (76.00)	6 (24.00)		
	3^	8 (66.67)	4 (33.33)		
	4^	18 (69.23)	8 (30.77)		
verbal GCS				0.242 (0.093, 0.631)[d]	**0.0026***
	1	36 (81.82)	8 (18.18)		
	2^	27 (90.00)	3 (10.00)		
	3^	13 (61.90)	8 (38.10)		
	4^	4 (50.00)	4 (50.00)		
	5^	1 (50.00)	1 (50.00)		
motor GCS					
	1	3 (100.00)	0 (0.00)	0.663 (0.264, 1.666)[e]	0.3807
	2	3 (75.00)	1 (25.00)		
	3	9 (75.00)	3 (25.00)		
	4^	27 (81.82)	6 (18.18)		
	5^	36 (76.60)	11 (23.40)		
	6^	3 (50.00)	3 (50.00)		
Rotterdam				NA	NA
	1	0 (--)	0 (--)		
	2	81 (77.14)	24 (22.86)		
	3	0 (--)	0 (--)		
	4	0 (--)	0 (--)		
	5	0 (--)	0 (--)		
	6	0 (--)	0 (--)		

^ = reference group, a = race was collapsed to compare whites to others, b = mechanism of injury was collapsed to compare MVC to other injuries, c = discharge location was collapsed to compare Home/Shelter vs. Acute/Sub-acute/Long-term Acute/Skilled Nursing/Assisted Living/Nursing Home Care vs. Morgue/Other/Hospice, d = verbal and motor GCS were collapsed into 1 vs > 1, e = motor GCS was collapsed into < 4 vs. > 4, * = significant at α = 0.05

Although no analysis was performed on this cohort of patients, the descriptive statistics for patients who exhibited an abnormal initial CT scan are included in the Appendix (Table S1).

The results of the initial domain automated procedures are detailed in Table 12. From this analysis, the variables that were chosen for selection into the final domain model were depression/suicidal thoughts, non-prescription drug abuse, race, verbal GCS score, glucose concentration, INR, pupil response, and decompressive craniectomy. The results of the automated procedures for the final model based on these initial domain results are shown in Table 13. Verbal GCS score was found to be significant in all three automated models while glucose concentration, decompressive craniectomy, and pupil response were additionally found to be significant in the forward selection procedure.

Table 12. Patient Characteristics selected into models based on automated model selection of domains for the normal CT cohort of patients (N = 105), F = forward selection, B = backward selection, SW = stepwise selection.

	Demographics / Social History	Exam / Lab / Imaging	Interventions / Surgeries
Variable			
Depression / Suicidal Thoughts	F/B/SW		
Non-Prescription Drug Abuse	F/B/SW		
Race	F/B/SW		
Verbal GCS		F/B/SW	
Pupil Response		F/B/SW	
Glucose		F/B/SW	
INR		F	
Decompressive Craniectomy			F/SW

Based on these results, the following three models were analyzed to ascertain a final parsimonious model for this cohort of normal CT patients by comparing the AIC, SC, and R^2. They include: 1) the final domain model from forward selection, 2) the final domain model from backward/stepwise selection, and 3) the final domain model from forward selection without the

decompressive craniectomy variable. The reason model 3 was selected for analysis was due to the sparseness associated with the decompressive craniectomy variable (Table 11). The results of this final selection procedure are detailed in Table 14.

Table 13. Patient characteristics selected into the models for the entire cohort of patients (N = 105) based on the Domain automated selection.

	Domain - Forward	Domain - Backward	Domain - Stepwise	Total
Variable				
Verbal GCS	X	X	X	3
Glucose	X			1
Decompressive Craniectomy	X			1
Pupil Response	X			1

Table 14. Model Statistics for assessing the final model that best predicts patient outcome in the cohort of patients with a normal CT scan. Model 1 = verbal GCS + glucose + decompressive craniectomy + pupil response, Model 2 = verbal GCS, Model 3 = verbal GCS + glucose + pupil response, AIC = Akaike Information Criterion, SC = Schwarz Criterion, R^2 = generalized coefficient of determination

Model	AIC	SC	R^2
1	98.869	121.662	0.2012
2	107.46	120.334	0.0867
3	103.205	123.465	0.1449

Since we are interested in the model with best combination of the lowest AIC, lowest SC, and highest R^2, model 1 was chosen as the best model of the data and takes the following form:

$$\begin{aligned} logit\,(p_i) = {} & -2.588 + 0.578 verbalGCS_2 - 1.446 verbalGCS_3 - 2.128 verbalGCS_4 \\ & - 1.466 verbalGCS_5 + 0.018 glucose - 16.743 decmp\_cran \\ & + 2.174 pupil_{bilateral} + 2.174 pupil_{unilateral} \end{aligned} \quad \text{(Model 2)}$$

The beta estimates standard, adjusted odds ratios, their 95% confidence intervals, and p-values are detailed in Table 15. Similarly to the entire patient cohort with respect to verbal GCS, the odds of a favorable GOS-E outcome was found to not be statistically different in patients with a GCS of 2 (OR = 1.782, CI_{95}: [0.359, 8.847], p-value = 0.4797) and a GCS of 5 (OR = 0.231, CI_{95}: [0.010, 1.036], p-value = 0.3622) but was found to be statistically significant in patients with a score of 3 (OR = 0.236, CI_{95}: [0.058, 0.961], p-value = 0.0439) and 4 (OR = 0.116, CI_{95}: [0.018, 0.725], p-value = 0.0213) compared to the verbal GCS reference score of 1. Additional patient characteristics that were found to be statistically significant in predicting favorable patient GOS-E outcome include patient initial glucose level (OR = 1.018, CI_{95}: [1.000, 1.036], p-value = 0.0496) and pupil response (bilateral vs. no response: OR = 8.789, CI_{95}: [1.076, 71.785], p-value = 0.0425, unilateral vs. no response: OR = 4.187, CI_{95}: [0.218, 80.357], p-value = 0.3421). While not statistically significant, whether or not the patient underwent a decompressive craniectomy procedure was included in the model (p-value = 0.9812).

Furthermore, a Hosmer-Lemeshow goodness of fit test of this model leads us to conclude that it fits the data well (χ^2 = 6.2096, df = 8, p-value = 0.6238) and therefore suggests a good fit exists between the observed and fitted values from the linear logistic model.

Table 15. Final Multivariable model that best predicts patient outcome for patients who exhibit a normal CT scan upon inclusion into the ProTECT III clinical trial.

Variable	Level	Beta	SE	Adjusted OR (CI_{95})	p-value
Verbal GCS					
	2 vs 1	0.5778	0.8175	1.782 (0.359, 8.847)	0.4797
	3 vs 1	-1.4459	0.7176	0.236 (0.058, 0.961)	0.0439
	4 vs 1	-2.1582	0.9373	0.116 (0.018, 0.725)	0.0213
	5 vs 1	-1.4656	1.6083	0.231 (0.010, 5.401)	0.3622
Glucose (mg/dL)		0.0175	0.00892	1.018 (1.000, 1.036)	0.0496
Decompressive Craniectomy	Yes vs No	-16.743	709.3	> 999.999 (0, ∞)	0.9812
Pupil Response					
	Bilateral vs No Response	2.1735	1.0715	8.789 (1.076, 71.785)	0.0425
	Unilateral vs No Response	1.4321	1.5074	4.187 (0.218, 80.357)	0.3421

Discussion

Interpretation of Results & Clinical Significance

Mirroring the results from the clinical trial, progesterone was found to be an ineffective treatment for acute TBI in patients with a normal CT scan. Possible explanations for the failure of efficacy are similar to those detailed for the entire cohort of patients. These include heterogeneity of disease, potential confounding pre-existing conditions, and characteristics of individual patterns, which were heavily-controlled for in the animal studies, yet proved to be too large of a role to overcome in human subjects.[32]

The patient characteristics that were associated with CT scan include age, depression/suicidal status, history of prescription drug, tobacco and alcohol abuse, discharge location, mechanism of injury, initial glucose level, verbal GCS, eye GCS, pupil response, intubation status, whether the patient had a cranial surgery, extracranial surgery, PEG tube installation, decompressive craniectomy, non intraventricular ICP monitor installation, tracheostomy, ventriculostomy, days in the ICU and hospital, and time to the emergency room. In general, the majority of these results are consistent with clinical findings.[50] One particularly interesting finding was that the proportion of patients with a history of prescription drug abuse was higher in the normal CT cohort of patients (11.8%) compared to the abnormal CT cohort of patients (3.8%). A similar counterintuitive finding was exhibited with respect to the proportion of patients who have a history of tobacco use (44.4% and 34.0% respectively).

Model 1 details the multivariable model for predicting patient outcome in the entire cohort of patients. Interestingly with regard to patient verbal GCS score, the odds of a favorable outcome is smaller for patients with a GCS score of 2, 3, 4, and 5 compared to a GCS of 1, meaning that patients who are better off initially do worse at 6 months. This departure from what we would expect is best explained by the sliding dichotomy depending on your initial diagnosis.

Patients with a poorer initial result don't need to improve as much as those who were better off initially. Age, ISS score both have a protective effect against a favorable GOS-E outcome. In addition, surgical procedures that also had a protective effect against a favorable GOS-E outcome include non-intraventricular ICP monitor installation and ventriculostomy. One particularly interesting finding was that patients with a previous TBI had better odds of favorable GOS-E outcome compared to those who had not had a previous injury indicating that the body and brain may be better prepared to second time a TBI occurs.

Model 2 details the multivariable model for predicting favorable patient GOS-E outcome in the cohort of patients with a normal CT scan. Similar to Model 1, verbal GCS is not only significant but also follows the same trend as the entire cohort in that odds of a favorable outcome is lower among those with scores of 3, 4, and 5 compared to a score of 1. Additional significant patient characteristics include a higher glucose level and bilateral and unilateral pupil responses compared to no pupil response. It is also worth commenting that the lack of precision associated with the odds ratios and point estimates is due to the inherently low sample size of this cohort of patients.

For the entire cohort of patients, three different model selection procedures were utilized to generate a total of seven different models for predicting patient outcome at 6 months. In the cohort of patients with a normal CT scan, a combination of two model selection procedures, the domain and automated selection, were used to develop two different models for predicting 6-month patient outcome. It is worth noting that there were some inherent differences in these models as a result of the various selection procedures. With respect to the three automated selection procedures, stepwise selection appears to be the strictest of the selection procedures. This can be explained by the fact that at each step of stepwise selection, each variable is

reevaluated for significance in the model. In forward selection and backward selection, less evaluation and reevaluation occur. Once a variable is deemed essential to the model, it remains in the model and is not further evaluated in combination with the other variables in the model. In addition, while there seems to be no inherent difference in the stringency of forward and backward model selection, many note that backward selection is the preferred method to forward selection. Since forward selection evaluates each predictor only when it is added in, that predictor added in at an earlier step in the process may become redundant once other predictors are added. Therefore, the final model may contain terms of little value. In backward selection, redundant variables would be inherently removed due to the nature of the selection process.

Of all of the model selection procedures that were utilized, the model selected based on Collett's deviance method contained the most predictors. One possible explanation of this could be due to the fact that a more conservative α value of 0.10 was used per Collett's recommendation instead of the stricter 0.05 value used in the automated selection procedures. Another possible explanation could be related to the large amount of predictors in the model. The pre-specified change in deviance (e.g., $X^2_{0.1,1}$= 2.71 or $X^2_{0.05,1}$ = 3.85) is independent of the number of predictors we are testing. With so many potential predictors in the model (and therefore a large deviance), dropping any of them individually from the model will induce enough of a change in the deviance to warrant keeping it in the model.

With regards to the domain selection procedure, it is interesting to note that even though this procedure utilized the automated selection procedures, similar yet slightly different final models were obtained. For example, six of the seven predictors chosen in the domain forward selection procedure were also chosen in the regular automated selection. Similar results exist upon comparison of the backwards and stepwise selections.

Limitations

It is worth noting that there are some limitations to this analysis. The largest limitation in the analysis took place in the model selection. SAS automatically drops observations with missing data before model selection takes place. The more potential predictors that exist in the model selection process, the more likely missing data will exist for observations in one or more of these predictors. Due to the nearly 40 predictors that were included as potential predictors of patient outcome that were included for model selection, a significant portion of the observations and their respective data were dropped before model selection even began. In the all-patient cohort model selection procedure, 335 out of the 829 (38.0%) of the observations were removed because of missing data. With respect to the normal CT cohort of patients, nearly half of the observations were removed due to missing data – 48 out of the 105 observations (45.7%). The removal of this data not only increases the standard errors and reduces the precision of our point estimates, but also could lead to biased findings. If the observations that are being dropped have some underlying characteristic in common, dropping these observations in favor of complete cases for the model selection will lead to biased results.

Another important limitation in this analysis was that initial blood alcohol concentrations (BAC) could not be determined and therefore could not be used as a potential predictor in the analysis. At randomization, BAC was supposed to be recorded in mg% but in many instances, was not properly recorded. Due to a wide range of implausible values for the initial BAC, this predictor was not able to be used. As a result, we are forced to generalize our results to patients with a blood ethanol concentration of less than 249 mg/dL as detailed by one of the exclusion criteria of the clinical trial (Figure 1).

Future Work

Future work should consider utilizing an imputation or interpolation technique to appropriately handle the large amount of missing data. It would also be beneficial to conduct a study using a larger cohort of patients who exhibited a normal initial CT scan. One could also consider conducting the same analysis on the patients who exhibited an abnormal CT scan and comparing the final model to the models that were generated for the entire cohort and the normal CT cohort of patients. Additional analyses involving fitting a model with appropriate interaction terms to assess if the effect of one patient predictor on the dichotomized outcome is different at different values of the other predictor patient predictor. Careful determination of the appropriate variables to interact via predetermined *a priori* clinical hypotheses would ensure the model is of reasonable length. Additionally, an analysis could be performed utilizing ROC curves to assess the accuracy of our prediction models.

Final Conclusions

While there are inherent limitations to this analysis, this work begins to add to the very limited literature related to predicting patient outcome in individuals with moderate and severe TBI. In these patients, those who are younger, with an normal initial CT scan, who do not undergo a ventriculostomy or non-intraventricular ICP monitor installation, with a low ISS, who have previously undergone a traumatic brain injury, and have an initial verbal GCS score of 3 or 4 are predicted to exhibit a better 6-month outcome than other patients without these characteristics. In patients who exhibit a normal initial CT scan, those with a higher baseline blood glucose concentration, a bilateral pupil response and an initial verbal GCS score or 3 or 4 are projected to have a better 6-month outcome than their counterparts.

Appendix

Table S1. Patient characteristics stratified by Dichotomized Outcome for patients with an abnormal CT upon admission into the ProTECT III clinical trial.

		Favorable Outcome	
		Yes n (%)	No n (%)
		n = 363	n = 361
		Missing = 32	
Variable			
Gender			
	Male	272 (51.22)	259 (48.78)
	Female	91 (47.15)	102 (52.85)
Intubated			
	Yes	109 (57.37)	81 (42.63)
	No	254 (47.57)	280 (52.43)
Ethnicity			
	Hispanic/Latino	60 (57.14)	45 (42.86)
	Not Hispanic/Latino	277 (49.20)	286 (50.80)
	Unknown	56	
Race			
	American Indian/Alaskan	3 (50.00)	3 (50.00)
	Asian	11 (33.33)	22 (66.67)
	Black/African American	51 (47.22)	57 (52.78)
	Native Hawaiian/Pacific Islander	1 (50.00)	1 (50.00)
	Caucasian	278 (50.73)	270 (49.27)
	Other	19 (70.37)	8 (29.63)
Mechanism of Injury			
	MVC	153 (60.47)	100 (39.53)
	Pedestrian In MVC	33 (33.00)	67 (67.00)
	Motorcycle/Moped	76 (52.05)	70 (47.95)
	Bicycle	22 (55.00)	18 (45.00)
	Fall < 3 feet	6 (31.58)	13 (68.42)
	Fall ≥ 3 feet	42 (41.58)	59 (58.42)
	Assault	15 (40.54)	22 (59.46)
	Blast	2 (100.00)	0 (0.00)
	Other	12 (57.14)	9 (42.86)
	Unknown	5	
Progesterone			
	Yes	177 (48.76)	186 (51.24)
	No	186 (51.52)	175 (48.48)
Discharge Location			
	Home	101 (69.18)	45 (30.82)

	Acute Facility	179 (64.16)	100 (35.84)
	Sub-acute Facility	25 (62.50)	15 (37.50)
	Long-term Acute	34 (45.33)	41 (54.67)
	Skilled Nursing	16 (41.03)	23 (58.97)
	Assisted Living	0 (--)	0 (--)
	Nursing Home Care	0 (0.00)	5 (100.00)
	Morgue	0 (0.00)	118 (100.00)
	Shelter	0 (0.00)	1 (100.00)
	Hospice	1 (16.67)	5 (83.33)
	Other	7 (46.67)	8 (53.33)
Cranial Surgery			
	Yes	190 (44.81)	234 (55.19)
	No	173 (57.67)	127 (42.33)
Extracranial Surgery			
	Yes	266 (52.26)	243 (47.74)
	No	97 (45.12)	118 (54.88)
Pupil Response			
	Unilateral	56 (47.06)	63 (52.94)
	Bilateral	297 (51.65)	278 (48.35)
	None	10 (33.33)	20 (66.67)
PEG Tube			
	Yes	103 (47.03)	116 (52.97)
	No	260 (51.49)	245 (48.51)
Decompressive Craniectomy			
	Yes	52 (35.37)	95 (64.63)
	No	311 (53.90)	266 (46.10)
Depression/Suicidal			
	Yes	49 (53.26)	43 (46.74)
	No	304 (50.00)	304 (50.00)
	Missing	24	
Non-Prescription Drug Abuse			
	Yes	83 (54.97)	68 (45.03)
	No	258 (48.68)	272 (51.32)
	Missing	43	
Prescription Drug Abuse			
	Yes	11 (45.83)	13 (54.17)
	No	311 (50.98)	299 (49.02)
	Missing	90	
Alcohol Abuse			
	Yes	90 (61.22)	57 (38.78)
	No	256 (48.39)	273 (51.61)

	Missing	48	
Hypotension			
	Yes	6 (46.15)	7 (53.85)
	No	357 (50.21)	354 (49.79)
Hypoxia			
	Yes	4 (57.14)	3 (42.86)
	No	359 (50.07)	358 (49.93)
Non-intraventricular ICP monitor (Camino, bolt)			
	Yes	65 (42.76)	87 (57.24)
	No	298 (52.10)	274 (47.90)
Schizophrenia			
	Yes	4 (30.77)	9 (69.23)
	No	349 (50.65)	340 (49.35)
	Missing	22	
Social History			
	Yes	174 (54.72)	144 (45.28)
	No	188 (47.12)	211 (52.88)
	Missing	7	
Spinal Stabilization / Cervical			
	Yes	10 (100.00)	0 (0.00)
	No	353 (49.44)	361 (50.56)
Prior TBI			
	Yes	42 (58.33)	30 (41.67)
	No	317 (49.61)	322 (50.39)
	Missing	13	
Tobacco			
	Yes	123 (53.02)	109 (46.98)
	No	222 (49.89)	223 (50.11)
	Missing	47	
Tracheostomy			
	Yes	118 (47.39)	131 (52.61)
	No	245 (51.58)	230 (48.42)
Ventriculostomy			
	Yes	108 (43.72)	139 (56.28)
	No	255 (53.46)	222 (46.54)
ISS		25.06 (11.24)	28.54 (10.89)
Days in ICU		11.69 (7.90)	12.23 (8.58)
Total Days in Hospital		17.10 (8.75)	16.03 (9.93)
Age (in years)		34.90 (15.31)	44.81 (19.21)
Glucose		149.84 (44.30)	157.54 (55.72)
Hemoglobin		13.80 (1.85)	13.38 (1.86)

INR		1.14 (0.63)	1.13 (0.27)
Time to Emergency Department (in min)		55.15 (27.84)	50.18 (26.69)
platelets		243.78 (72.22)	249.26 (71.20)
eye GCS			
	1	216 (54.68)	179 (45.32)
	2	47 (49.47)	48 (50.53)
	3	43 (46.24)	50 (53.76)
	4	57 (40.43)	84 (59.57)
verbal GCS			
	1	213 (55.61)	170 (44.39)
	2	100 (47.85)	109 (52.15)
	3	28 (37.33)	47 (62.67)
	4	18 (35.29)	33 (64.71)
	5	4 (66.67)	2 (33.33)
motor GCS			
	1	10 (76.92)	3 (23.08)
	2	33 (57.89)	24 (42.11)
	3	47 (51.09)	45 (48.91)
	4	118 (49.79)	119 (50.21)
	5	146 (47.40)	162 (52.60)
	6	9 (52.94)	8 (47.06)
Rotterdam			
	1	8 (61.54)	5 (38.46)
	2	108 (60.00)	72 (40.00)
	3	203 (53.85)	174 (46.15)
	4	26 (34.67)	49 (65.33)
	5	16 (23.88)	51 (76.12)
	6	2 (16.67)	10 (83.33)

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