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Presenting characteristics associated with outcome in children with severe traumatic brain injury: a secondary analysis from a randomized, controlled trial of therapeutic hypothermia

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Abstract

Objective—To identify injury patterns and characteristics associated with severe traumatic brain injury (TBI) course and outcome, within a well-characterized cohort, which may help guide new research and treatment initiatives.

Design—A secondary analysis of a phase 3, randomized, controlled trial that compared therapeutic hypothermia versus normothermia following severe TBI in children.

Setting—Fifteen sites in the United States, Australia and New Zealand.

Patients—Children (<18 years old) with severe TBI.

Measurements and Main Results—Baseline, clinical and computed tomography (CT) characteristics of patients (n=77) were examined for association with mortality and outcome, as measured by the Glasgow Outcome Scale-Extended Pediatrics (GOS-E Peds) 3 months after TBI.

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Data are presented as odds ratios with 95% confidence intervals (OR [95% CI]). No demographic, clinical or CT characteristic was associated with mortality in bivariate analysis. Characteristics associated with worse GOS-E Peds in bivariate analysis were two fixed pupils (14.17 [3.38–59.37]), abdominal abbreviated injury severity (AIS) score (2.03 [1.19–3.49]), and subarachnoid hemorrhage (3.36 [1.30–8.70]). Forward stepwise regression demonstrated that AIS spine (3.48 [1.14–10.58]) and midline shift on CT (8.35 [1.05–66.59]) were significantly associated with mortality. Number of fixed pupils (one fixed pupil 3.47 [0.79–15.30]; two fixed pupils 13.61 [2.89–64.07]), hypoxia (5.22 [1.02–26.67]) and subarachnoid hemorrhage (3.01 [1.01–9.01]) were independently associated with worse GOS-E Peds following forward stepwise regression.

Conclusions—Severe traumatic brain injury (TBI) is a clinically heterogeneous disease that can be accompanied by a range of neurologic impairment and a variety of injury patterns at presentation. This secondary analysis of prospectively collected data identifies several characteristics associated with outcome among children with severe TBI. Future, larger trials are needed to better characterize phenotypes within this population.

Keywords

pediatric traumatic brain injury; outcomes; phenotype; prediction; subarachnoid hemorrhage; fixed pupils

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability throughout the world and is associated with a high economic burden, with reported annual cost estimates in the United States ranging from $56 billion to $221 billion (2009 USD)(1). Significant research efforts have led to progress in the care of severe TBI, though breakthrough treatments remain elusive. Recent randomized controlled trials have failed to show a benefit for previously promising therapies, including progesterone, erythropoietin, and hypothermia (2–4). Reexamination of such well-conducted negative trials has brought attention to some of the intrinsic difficulties associated with adequately categorizing TBI patients for the purposes of directing both clinical research and contemporary treatment strategies (5).

The post-resuscitation Glasgow Coma Scale (GCS) score has been associated with outcome in childhood severe TBI and is the current standard for measuring injury severity in such patients (6). The Brain Trauma Foundation 2012 guidelines for management of childhood severe TBI inclusion criteria are selective for patients with a GCS < 9, as do most scientific publications within the field (7). However, severe TBI is a heterogeneous disease and is commonly accompanied by a spectrum of additional injuries and co-morbidities. A better understanding of injury patterns and patient characteristics associated with disease course and outcome would aid present-day management, future study design, and is necessary to identify unique phenotypes of TBI. The Cool Kids Trial was a multi-national randomized, controlled trial examining the effect hypothermia versus normothermia on mortality in children with severe TBI but was halted early for futility. We performed a secondary analysis of the aggregate, prospectively collected cohort, with the aim of identifying presenting patient characteristics and head computed tomography (CT) findings associated with outcome among children with severe TBI.

Methods

Study Design

The Cool Kids Trial was a phase 3, multi-national, randomized, controlled trial designed to assess the efficacy of early, moderate hypothermia (32 – 33°C) with slow rewarming on mortality after severe TBI in children (3). The study was conducted across 15 centers in the United States, New Zealand and Australia. Enrollment criteria included children less than 18 years of age who sustained non-penetrating brain injury, a post-resuscitation GCS less than 9 and a GCS motor score of less than 6 who were available for randomization within 6 hours of injury. Exclusion criteria were a normal head CT scan, post-resuscitation GCS of 3 with concomitant unreactive pupils, non-accidental trauma, hypotension for more than 10 minutes (defined as systolic blood pressure less than 5th percentile for age), uncorrectable coagulopathy, hypoxia (defined as oxygen saturation less than 90% for greater than 30 minutes after resuscitation), abbreviated injury severe score (AIS) greater than 3 for organs other than the brain, or suspected pregnancy. The Institutional Review Boards of each participating center approved the protocol and required either informed written consent or allowed emergency waiver of consent (5 of the 15 study sites).

Demographic and clinical data were obtained upon trial entry. Patients randomized to hypothermia were rapidly cooled to 32–33°C and maintained for 48 hours, then slowly rewarmed by 0.5–1°C every 12–24 hours as part of a slow rewarming protocol. An additional 24 hours of hypothermia was maintained if intracranial pressure (ICP) was elevated at 48 hours, with subsequent slow rewarming irrespective of ICP levels. Therapeutic goals for all patients centered around avoiding hypotension, hypoxia and intracranial hypertension. The planned sample size for the trial was 340 patients; however, the study was stopped by the Data Safety Monitoring Board after 77 patients were enrolled due to futility.

Computed Tomography (CT) Imaging

Patients underwent head computed tomography (CT) imaging as part of the initial evaluation and images were transferred to the Data Coordinating Center at the University of Pittsburgh. Clinical interpretations by site personnel were used to assess for inclusion into the study. For this secondary analysis, 3 pediatric radiologists independently assessed the images for injuries – with each subject's scans read by 2 radiologists. Discrepancies between the independent assessments of the 2 readers were recorded and resolved by consensus. Data collection was in accordance with the National Institute of Neurological Disorders and Stroke Common Data Elements for Neuroimaging and readers were instructed to categorize findings as present, absent or indeterminate for each of the following data fields: skull fracture, extra axial hematoma, epidural hematoma, subdural hematoma, intracerebral hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, supratentorial midline shift, cisternal compression, fourth ventricle shift or effacement, diffuse axonal injury (DAI), contusion, penetrating injury, cervicomedullary junction or brainstem injury, brain swelling, and ischemia, infarction or hypoxic-ischemic injury (see Supplementary Material)(8,9).

Outcomes and Statistical Analysis

The main outcomes of this study were mortality and Glasgow Outcome Score Extended Pediatric Revision (GOS-E Peds) assessed at 3 months after injury. The GOS-E Peds is an eight-point scale, ranging from 1 (upper good recovery) to 8 (death), designed to assess outcome after TBI in children. Because of limited sample size, the GOS-E Peds was reduced to a three-point ordinal scale for all the statistical analyses by collapsing three and four levels [GOS-E Peds: 1–4 (1), 5–7 (2) and 8 (3)], as previously reported (10).

Descriptive statistics were summarized as median and interquartile range (IQR) or frequencies and percentages for continuous and categorical data, respectivelyBivariate logistic regression was applied to assess the strength of association between baseline, clinical or CT characteristics (e.g. age, GCS score, etc.) and the dichotomous outcome of interest (i.e. mortality). Hypoxia and hypotension were identified as characteristics if present but were not sustained long enough to achieve trial exclusion criteria. Apnea and aspiration were identified clinically per the discretion of the site principal investigator and reported as adverse events into the database. Bivariate proportional odds regression models were used to assess the strength of association between baseline, clinical and CT Characteristics (e.g. age, GCS score, etc.) and the ordinal outcome of interest (e.g. GOS-E Peds). Separate bivariate analyses examined whether a differential effect existed for either morality or dichotomized GOS-E Peds based on trial arm (hypothermia versus normothermia). The magnitude of associations between the potential predictor variables and each outcome was quantified using the odds ratio (OR) and the corresponding 95% confidence interval (CI). Any predictor variable with a $p < 0.25$ for the Wald statistic were selected for model fitting in a subsequent multiple logistic regression or multiple proportional odds regression analysis using a forward stepwise approach. The level of significance to enter or remain in the model was set to 0.10 and 0.05, respectively. Odds ratios and 95% CIs were calculated from the beta coefficients. Pearson's correlation coefficient was computed to determine the association between independent variables of interest included in the multivariable regression models. Variance inflation factors were also estimated from multivariable regression models to assess potential multicollinearity. Performance of the logistic regression models was tested by means of Hosmer-and-Lemeshow goodness-of-fit test. Performance of the proportional odds regression models was tested by means of Deviance and Pearson goodness-of-fit statistics. All analyses were two-sided and the alpha level was set to 0.05. Analyses were conducted using SAS, version 9.3 statistical software (SAS Institute Inc., Cary, NC).

Results

The analysis included all 77 children who underwent randomization during the trial which consisted of 48 (62%) males with a median age of 11 years (IQR 3 – 15) at the time of injury. GOS-E Peds data were available for 73 subjects. Overall, 40 subjects (55%) were stratified into the favorable outcome group (GOS-E Peds 1–4) with 27 (37%) surviving with an unfavorable outcome (GOS-E Peds 5–7) and 6 (8%) deaths (GOS-E Peds 8).

Descriptive statistics for patient demographics and baseline clinical attributes and their association with outcomes in bivariate analysis are summarized in Table 1. Among the 77

patients, 14 (18%) and 19 (25%) patients showed elevated AIS scores for spine and abdominal regions, respectively. No baseline or clinical attribute was significantly associated with mortality in bivariate analysis. GCS total score (OR 0.53 [95%CI 0.35–0.79]), AIS abdomen (OR 2.03 [1.19–3.49]) and number of fixed pupils (one fixed pupil OR 3.42 [0.89–13.22]; two fixed pupils OR 14.17 [3.38–59.37]) were significantly associated with GOS-E Peds. Stratifying the analyses into hypothermia and normothermia groups did not demonstrate any significant differential effects for characteristics associated with outcome in the aggregate cohort (Supplemental Tables 1 and 2).

Head CT images were available for 75 patients. Before consensus, the overall average percent agreement between the radiologists across all CT findings for all patients was excellent (range 83.6–90.6%), and agreement between radiologists was poor to excellent (kappa statistic = −0.05–1.00). The intra-rater analysis showed that the overall average percent agreement across all CT findings was substantial (range 83.1–90.8%). Table 2 shows the frequency distribution of the CT findings and their association with outcomes in bivariate analysis. The most common intracranial CT abnormalities were skull fracture, extra axial hematoma, subdural hematoma, intracerebral hemorrhage and subarachnoid hemorrhage. No individual CT finding was associated with mortality. Subarachnoid hemorrhage was associated with GOS-E Peds (OR 3.36 [1.30–8.70]).

Pearson’s correlation coefficient between independent variables of interest included in the multivariable regression models ranged from −0.32 to 0.46. Table 3 summarizes the results of the forward stepwise regression analyses. AIS spine and midline shift were independently associated with mortality in a multivariable stepwise regression model. Subarachnoid hemorrhage, hypoxia and the number of fixed pupils were independently associated with poor outcome as measured by 3-month GOS-E Peds.

Discussion

In this secondary analysis of a well-described cohort of subjects from the Cool Kids trial, we identified several baseline characteristics and injury types associated with outcomes. Bivariate analysis of the present cohort demonstrated an association between AIS abdomen, GCS, subarachnoid hemorrhage and pupillary reaction, and GOS-E Peds. In multivariable analysis, hypoxia sustained for less than 10 minutes, subarachnoid hemorrhage, and presence of bilateral unreactive pupils were significantly associated with poor outcome as indicated by GOS-E Peds. In addition, higher AIS spine severity score and presence of midline shift were associated with mortality. For the purposes of the initial trial, data were recorded prospectively soon after injury across multiple international centers, strengthening the observed associations between the injury patterns and characteristics identified in this study as associated with outcome in severe TBI and furthering efforts to personalize approaches to investigation and care of this population.

Both secondary brain injury and accompanying organ trauma are important determinants of outcome in patients with TBI. Hypoxia, hypotension, seizures and extracranial injuries have been associated with worse outcomes (11–14). Hypoxia is a known determinant of outcome in childhood TBI and its presence in the pre-hospital setting has been associated with

mortality (15). The prevalence of hypoxia in 13% of this cohort is comparable to the occurrence of hypoxia in 17% reported in a recent analysis of the Pediatric Guideline Adherence and Outcomes (PEGASUS) cohort (13). That same study reported that all patients received timely treatment of hypoxia, reflecting clinical vigilance that may favorably reduce the measurable association between hypoxia and outcome in children with TBI. Patients hypoxic for more than 30 minutes were excluded from the Cool Kids trial. Accordingly, the observed association between hypoxia and outcome in the present study suggests that even relatively short periods of hypoxia are likely influential in determining outcome among children with severe TBI.

Injury patterns on head CT are also known to have prognostic implications in TBI (16). Radiologist evaluations in the present study demonstrated poor to excellent agreement, as measured by kappa, but excellent percent agreement. Previous studies have demonstrated this paradox of low kappa but high percent agreement, which occurs in situations of symmetric imbalance between two assessors and indicates the need to interpret kappa in the context of percent agreement rather than as a sole metric of agreement (17). Subarachnoid hemorrhage has been previously shown to be an independent predictor of worse outcome in children with TBI, as compared to other hemorrhage patterns (18,19). Subarachnoid hemorrhage is associated with high energy injury mechanisms conferring overall worse initial brain injury (20). Traumatic subarachnoid hemorrhage is also associated with deleterious vasospasm, though data regarding the prevalence of this phenomenon in children are scarce (21,22). Basilar skull fractures also occur with high energy mechanisms, are associated with subarachnoid hemorrhage and have been independently associated with mortality in children with severe TBI (23). Skull fractures were not associated with outcome in the present analysis, though the CT grading system did not distinguish basilar and non-basilar fractures.

Pupillary reaction has been associated with outcome in studies of both adult and pediatric severe TBI (11,24). However, a recent retrospective cohort study found better outcomes in children compared to adults with severe TBI, even amongst patients with fixed pupils and GCS score 3 (25). The association observed in the present cohort between the number of fixed pupils and 3-month outcome suggests that presenting pupillary reaction is prognostic in pediatric severe TBI, though caution is warranted in assigning comparable predictive weight to this finding as compared to adult patients. The ORs for bilateral unreactive pupils of 7.83 for mortality in bivariate analysis is substantial, yet lower than ORs for mortality reported by other studies, and pupillary response was not associated with mortality in this study. Other notable multivariable models have demonstrated significant ORs of 20.7, 60.38, 34.51 and 30.47, respectively.(14,18,23,26) The exclusion of patients with GCS 3 and unreactive pupils, as well as the low number of deaths, likely resulted in the lower OR in the present study. This is further evidenced by the lack of association between GCS and outcome, despite a strong association having been demonstrated in multiple other studies (14,18,23,26,27).

AIS spine and midline shift were associated with mortality in multivariable analyses. A corollary of the relationship between spine injury and mortality has been previously reported; in a review of studies examining patients with traumatic atlanto-occipital

dislocation, only TBI was predictive of death. The presence of spinal cord injury, polytrauma, and severity of dislocation according to a classification system were not associated with mortality (28). Similarly, an examination of 10 years of trauma registry data from South Carolina also demonstrated TBI as an independent predictor of mortality in patients with spine injury, as did a retrospective review of 33 trauma patients from a single center in the Southwestern United States (29,30). A separate registry review reported clinically significant cervical spine injuries in 9% of children with severe TBI and 11% of children suffering in-hospital trauma deaths (31).

Midline shift has previously been associated with mortality in patients with severe TBI and has been incorporated into validated multivariable models for prognostication of adult patients with severe TBI (32). Among children with penetrating head injuries, the absence of midline shift is a favorable prognostic sign (33). In a study of 100 children with severe head injury in India, midline shift was associated with 24 hour mortality in bivariate analysis, but only brain edema emerged as a significant predictor in multivariable analysis (34). The magnitude of midline shift can be determined by both the volume of extra-axial blood, as well as regional parenchymal edema. A recent study of 59 adult patients noted that midline shift greater than 3 mm in excess of the thickness of extra-axial blood apparent on initial head CT was associated a positive predictive value of 1.0 for mortality (35). Further evaluation in children is warranted to determine whether similar measurements may further discriminate the prognostic implications of midline shift.

Children with suspected abusive head trauma were excluded from the original Cool Kids trial because injury timing in this group can be difficult to discern and acute-on-chronic insults are well-described. Despite this exclusion, the enrolled cohort sustained a range of types of head and body trauma. The need to address complex heterogeneity present in TBI trial design and clinical management is well-recognized. The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) study merged patient data from eight randomized controlled trials and three observational surveys to create prognostic models providing improved covariate adjustment and risk stratification for TBI patients as young as 14 years (36). Compared to older adolescents and adults, far fewer trials exist for younger children with severe TBI and the influence of potentially important demographic, injury and illness characteristics on outcome is less clear. For the most recent iteration of the guidelines for the management of severe TBI in children, insufficient evidence existed to make a Level I recommendation for any of the topics and only four Level II recommendations were made for other therapies.(7)

Distinct phenotypes are emerging for sepsis, asthma, and acute respiratory distress syndrome, among other diseases (37–39). Within severe TBI, identifying patient-level characteristics associated with outcome provides a step towards better understanding the pathobiological features of brain and accompanying organ trauma that offer the highest-impact therapeutic targets in this population. Distinguishing phenotypes of severe TBI also has important implications for defining clinical trial cohorts. For example, the results of the present analysis suggest that trial arm imbalances in the prevalence of subarachnoid hemorrhage or the presence of midline shift may confound an observed treatment effect, despite adequately accounting for other markers of illness severity such as AIS score. Larger

cohort sizes than the present study are necessary to further investigate the associations observed in the present analysis and to identify other features of children with TBI worthy of subcategorization into discrete phenotypes. Analytic approaches such as cluster analysis that aim to reduce big, granular datasets into groups characterized by distinct features are increasingly used to identify disease phenotypes (40). The ongoing Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial to evaluate the impact of various interventions on the outcomes of children with severe TBI may eventually lead to new insights regarding the effect of these factors on outcomes.

Strengths of the present analysis include the prospective nature of the data collection and the original multicenter design. Excluding patients demonstrating early evidence of brain death (GCS 3 and unreactive pupils), that may ultimately lead to the diagnosis of “death by neurological criteria”, as well as those experiencing sustained periods of hypoxia and hypotension, led to a cohort representing a subset of post-resuscitation children with severe TBI. Outcomes for this group are thought to be more dependent on post-resuscitation care and therefore less confounded by grave injuries or early, significant secondary injury. This analysis is limited by the relatively small size of the study cohort secondary to the early cessation of the original Cool Kids trial. This study represents a secondary analysis and there was no *a priori* attempt to ensure sufficient power for examining associations between outcome and the analyzed patient factors. Management of intracranial hypertension was prescribed in the trial and preceded the most recent iteration of the guidelines for management of severe TBI in children, though it’s unclear whether current recommendations would substantially alter the identified risk factors for poor outcome. Factors not examined in the original trial but potentially related to outcome, such as blood transfusions, could not be studied in this analysis (14). Generalizability is also somewhat limited by the distribution of study site enrollment. While the study was conducted at 30 international centers, a majority of patients were enrolled at three sites (University of Pittsburgh, University of California/Davis, and University of Texas-Southwestern), raising the possibility that data are reflective of center-specific practices. The results from this study should be interpreted with caution due to the limited sample size and limited number of outcome events (i.e. 6 deaths).

In conclusion, the present analysis of a randomized, controlled trial enrolling children with severe TBI shows a significant association between mortality and both spine injury and midline shift in children with TBI. Additionally, among multiple clinical and head CT characteristics, the number of fixed pupils, hypoxia and presence of subarachnoid hemorrhage were associated with GOS-E Peds at 3-month follow-up. GCS total score was not associated with either mortality or GOS-E Peds in multivariable regression models in the present study. Together, these findings indicate the need for additional, larger studies in the arena of childhood severe TBI to further define phenotypes of this population by clarifying patient characteristics important for risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline and clinical characteristics and outcomes

Characteristic	Median (IQR) or N(%)	MortalityOR (95% CI)	*P*	GOS-E PedsOR (95% CI)	*P*
Age (years)	11 (3–15)	0.95 (0.82, 1.11)	0.51	1.00 (0.93, 1.09)	0.93
Sex (male)	48 (62%)	0.56 (0.10, 2.98)	0.50	0.64 (0.25, 1.61)	0.34
Ethnicity (Hispanic)	16 (21%)	0.83(0.09, 7.73)	0.87	0.88 (0.28, 2.78)	0.83
Height (cm)	1.4 (1.0–1.7)	0.99 (0.97, 1.01)	0.35	1.00 (0.99, 1.01)	0.74
Weight (Kg)	32 (16–60)	0.99 (0.96, 1.03)	0.71	0.99 (0.98, 1.01)	0.51
BMI (Kg/m^2)	19 (16–21)	1.01 (0.91, 1.13)	0.83	0.93 (0.85, 1.03)	0.16
GCS Score	6 (5–7)	0.77 (0.39, 1.50)	0.44	0.53 (0.35, 0.79)	<0.01
AIS					
Head	4 (4–5)	1.05 (0.37, 2.95)	0.93	1.29 (0.74, 2.27)	0.37
Face	1 (0–2)	0.53 (0.17, 1.61)	0.26	1.22 (0.75, 1.98)	0.43
Neck	0 (0–0)	*	*	0.53 (0.09, 2.95)	0.46
Thorax	0 (0–2)	1.49 (0.84, 2.63)	0.17	1.24 (0.87, 1.76)	0.24
Abdomen	0 (0–0)	1.55 (0.72, 3.33)	0.26	2.03 (1.19, 3.49)	0.01
Spine	0 (0–0)	2.46 (0.97, 6.21)	0.06	1.42 (0.74, 2.74)	0.29
Upper Extremities	0 (0–1)	*	*	0.88 (0.46, 1.70)	0.71
Lower Extremities	0 (0–1)	1.03 (0.43, 2.43)	0.95	1.41 (0.88, 2.25)	0.15
External	0 (0–0)	1.47 (0.25, 8.76)	0.67	1.17 (0.42, 3.23)	0.76
Left Pupil Size (mm)	3 (2–4)	0.99 (0.50, 1.95)	0.98	0.97 (0.67, 1.40)	0.86
Right Pupil Size (mm)	3 (2–4)	1.52 (0.91, 2.56)	0.11	1.04 (0.74, 1.45)	0.83
Number of Fixed Pupils			0.11		< 0.001
None	52 (69%)				
Unilateral	11 (15%)	2.61 (0.21, 31.94)		3.42 (0.89, 13.22)	
Bilateral	12 (16%)	7.83 (1.14, 53.76)		14.17 (3.38, 59.37)	

Characteristic	Median (IQR) or N(%)	MortalityOR (95% CI)	*P*	GOS-E PedsOR (95% CI)	*P*
Complications					
Apnea	6 (8%)	*	*	4.38 (0.75, 25.62)	0.10
Aspiration	12 (16%)	1.14 (0.12, 10.81)	0.98	2.87 (0.83, 9.94)	0.10
Cardiac Arrest	2 (3%)	*	*	*	*
Hypotension	6 (8%)	*	*	1.43 (0.25, 8.13)	0.69
Hypoxia	10 (13%)	*	*	4.76 (1.02, 22.13)	0.05
Seizure	12 (16%)	*	*	0.50 (0.14, 1.85)	0.30

GOS-E Peds = Glasgow Outcome Scale – Extended Pediatric Revision; BMI = body mass index; GCS = Glasgow Comma Scale; AIS = Abbreviated Injury Severity; IQR = interquartile range; OR = odds ratio; CI = confidence interval;

*Quasi–complete separation of data points detected, may be due to sparse data

Table 2

Computerized Tomography findings and outcomes

Characteristics	**N(%) [Indeterminate N(%)]**	**Mortality OR (95% CI)**	***P***	**GOS-E Peds OR (95% CI)**	***P***
Skull Fracture	41 (55%)	1.67 (0.29, 9.74)	0.57	1.49 (0.59, 3.71)	0.40
Extra axial hematoma	53 (71%)	2.17 (0.24, 19.82)	0.49	1.26 (0.46, 3.44)	0.65
Epidural hematoma	8 (11%)	1.69 (0.17, 16.57)	0.65	0.41 (0.08, 2.07)	0.28
Subdural hematoma	49 (65%)	2.86 (0.32, 25.90)	0.35	2.45 (0.90, 6.67)	0.08
Intracerebral hemorrhage	42 (56%)	1.67 (0.29, 9.74)	0.57	1.82 (0.72, 4.59)	0.20
Intraventricular hemorrhage	22 (29%)	1.24 (0.21, 7.33)	0.81	2.22 (0.83, 5.97)	0.11
Subarachnoid hemorrhage	40 (53%)	5.31 (0.59, 47.98)	0.14	3.36 (1.30, 8.70)	0.01
Midline shift	23 (31%)	4.95 (0.84, 29.31)	0.08	1.12 (0.43, 2.95)	0.81
Cisternal compression	18 (24%)	0.58 (0.06, 5.29)	0.63	0.88 (0.31, 2.51)	0.81
Fourth ventricle shift	7 (9%) [1 (1%)]	*	0.85	1.78 (0.40, 7.92) 3.96 (0.09, 169.51)	0.59
Diffuse axonal injury	17 (23%) [48 (64%)]	*	0.93	7.39 (1.17, 46.51) 2.65 (0.49, 14.29)	0.06
Contusion	36 (48%) [2 (3%)]	*	1.00	1.00 (0.40, 2.50) 1.00 (0.06, 16.13)	1.00
Penetrating injury	0 (0%)				
Cervicomedullary junction or brainstem injury	1 (1%) [2 (3%)]	*	1.00	*	0.63
Edema	20 (27%) [2 (3%)]	*	0.84	2.04 (0.74, 5.67) 1.24 (0.08, 19.67)	0.39
Brain swelling	18 (24%) [2 (3%)]	*	0.39	1.94 (0.69, 5.47) 1.18 (0.08, 18.69)	0.45
Ischemia or infarction or hypoxic-ischemic injury	4 (5%) [4 (5%)]	*	0.55	1.09 (0.14, 7.82) 4.00 (0.57, 28.04)	0.38
Brain atrophy	0 (0%)				

GOS-E Peds = Glasgow Outcome Scale – Extended Pediatric Revision; OR = odds ratio; CI = confidence interval;

*Quasi–complete separation of data points detected, may be due to sparse data

Table 3

Summary of forward stepwise regression models

Outcome of Interest	Characteristic	OR (95% CI)	*P*
Mortality	AIS SpineMidline shift	3.48 (1.14, 10.58)8.35 (1.05, 66.59)	0.030.045
GOS-E Peds	Number of Fixed Pupils (reference: None)		
	Unilateral	3.47 (0.79, 15.30)	0.10
	Bilateral	13.61 (2.89, 64.07)	0.001
	Hypoxia	5.22 (1.02, 26.67)	0.047
	Subarachnoid hemorrhage	3.01 (1.01, 9.01)	0.049

GOS-E Peds = Glasgow Outcome Scale – Extended Pediatric Revision; AIS = Abbreviated Injury Severity