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Age and Mortality in Pediatric Severe Traumatic Brain Injury: Results from an International Study

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Abstract

Background: Although small series have suggested that younger age is associated with less favorable outcome after severe traumatic brain injury (TBI), confounders and biases have limited our understanding of this relationship. We hypothesized that there would be an association between age and mortality in children within an ongoing observational, cohort study.

Methods: The first 200 subjects from the Approaches and Decisions for Acute Pediatric TBI (ADAPT) trial were eligible for this analysis (inclusion criteria: severe TBI [GCS ≤ 8], age 18 y, ICP monitor placed; exclusion: pregnancy). Children with suspected abusive head trauma (AHT) were excluded to avoid bias related to the association between AHT and mortality. Demographics, prehospital and resuscitation events were collected/analyzed and children were stratified based on age at time of injury (< 5y, 5 -<11y, 11–18y) and presented as mean ± SEM. Analyses of variance were used to test the equality of the means across the group for continuous variable and chi-square tests were used to compare percentages for discrete variables (post hoc comparisons were performed using t-test and Bonferroni corrections, as needed). Kaplan-Meier curves were generated for each age subgroup describing the time of death and log-rank was used to compare the curves. Cox proportional hazards regression models were used to assess the effect of age on time to death while controlling for covariates.

Results: In the final cohort (n = 155, 45 excluded for AHT), overall age was 9.2 y ± 0.4 and GCS was 5.3 ± 0.1. Mortality was similar between strata (14.0%, 20.0%, 20.9%, respectively, p = 0.58). Motor vehicle accidents were the most common mechanism across all strata while falls tended to be more common in the youngest stratum (p = 0.08). The youngest stratum demonstrated and increased incidence of spontaneous hypothermia at presentation, decreased hemoglobin concentrations and coagulopathies, while the oldest demonstrated lower platelet counts.

Conclusions: In contrast to previous reports, we failed to detect mortality differences across age strata in children with severe TBI. We have discerned novel associations between age and various markers of injury – unrelated to AHT - that may lead to testable hypotheses in the future.

Keywords

pediatric traumatic brain injury; age; comparative effectiveness research; pediatric neurocritical care; secondary injuries

Introduction

Traumatic brain injury (TBI) is the leading cause of trauma-related death and permanent disability. According to the CDC, an estimated 1.7 million TBIs occur in the US annually with a tri-modal distribution of incidence - children 0 – 4 y, adolescents 15 – 19 y and adults > 65 y – at highest risk (1). Over the past decade, TBI-related emergency department visits increased by 70% (2). Among children in the United States, TBI was responsible for 7440 deaths, 60,000 hospitalizations, and 600,000 emergency visits (3). The economic burden of pediatric TBI is estimated to exceed $50 billion annually (3). The Brain Trauma

Foundation released guidelines for the management of severe pediatric TBI (4, 5), yet there is considerable management variability among practitioners of pediatric TBI (6). In 2011, an international collaboration recommended a comparative effectiveness research approach with the overarching goal of improving and standardizing TBI management (7). Fundamental to achieving this goal is to understand how TBI affects children across the age spectrum.

The association between age and outcome after TBI in children is poorly understood. It has been theorized that the plasticity of the immature brain could allow adaptations to the initial insults – leading to improved overall outcomes or even survival from severe injuries. This has not been borne out by the existing literature (8) as younger age has often been associated with worse outcome (9–11). An analysis of 103 children with severe TBI revealed lower post-resuscitation Glasgow Coma Scores, more frequent hypotension and higher mortality among children <4y (12). However, a single-center series of children with severe TBI showed children <5y had *better* outcomes (13), while another spanning the entire injury range also found better outcomes in infants (14).

An important consideration in the assessment of age on outcomes in children with severe TBI is the confounding factor of abusive head trauma (AHT). Children with AHT likely have delay in seeking medical care, have less reliable medical historians and may have chronic injuries. AHT has been shown to carry a worse prognosis than accidental TBI (15–18). Similarly, previous studies of young children that showed a worse outcome for the youngest age group included both accidental injuries and AHT (12, 19). To study the effect of age alone on mortality - as well the association with other clinical events - we chose to exclude children with AHT from our analysis.

We hypothesized that there was a relationship between age and mortality in children with severe TBI. To test this hypothesis, we analyzed data from the first 200 children of the Approaches and Decisions for Acute Pediatric TBI (ADAPT) trial. Secondarily, we assessed the association of injury characteristics and prehospital/resuscitation events and age.

Methods

The ADAPT trial is a comparative effectiveness study of children with severe TBI funded by a cooperative agreement with NINDS (U01 NS 081041). The overall goal of the study is to compare the effectiveness of strategies related to intracranial hypertension, secondary injuries and metabolic support in 1000 children from multiple centers within the US and abroad. All sites obtained Institutional Review/Ethics Board approval and the University of Pittsburgh received IRB approval to coordinate the study. The design of the ADAPT Trial is observational – sites care for children based on their local standards without any study-based interventions. Because of this study design and the scientific need to avoid without selection bias, all clinical sites were granted permission to collect data regarding the acute hospitalization on all children meeting inclusion/exclusion criteria (inclusion: age < 18 y, diagnosis of severe TBI [Glasgow Coma Scale {GCS} score ≤ 8], placement of intracranial pressure [ICP] monitor at study site; exclusion: pregnancy). Informed consent was obtained for follow-up activities. Therefore, the subjects within the overall study and

this report represent *consecutive eligible subjects admitted to study sites*. Mortality was defined as death within the study period.

The first 200 subjects enrolled in the ADAPT trial (February 22, 2014 – December 22, 2014) were studied. The analysis was intended to determine the factors associated with mortality in children with different mechanisms of injury – with a focus on the age of the subjects. Demographic characteristics, injury details/scores (Abbreviated Injury Scores [AIS], Injury Severity Scores [ISS], Pediatric Risk of Mortality [PRISM] III scores), prehospital events and resuscitation events were analyzed. Definitions of these variables are provided within the Supplementary table. Mortality and the cause of death as indicated by the medical records were identified. Prehospital events were defined as events that occurred from the time the injury until presentation to the study hospital. Resuscitation phase of care was defined as from the time of admission to the clinical site until the ICP monitor was placed.

Data Stratification and Data Analysis

The age of subjects was defined at the time of ICP monitor placement. Children were stratified by age: <5y, 5 -<11y and 11-<18 y. Children with any likelihood of child abuse were excluded. Briefly, clinical sites were asked to stratify children of any age based on the likelihood of abuse, as we have previously published. For this analysis, children with “Definite”, “Probable” and “Possible” child abuse were excluded from this analysis (“Definite” indicates that medical record review demonstrates that the medical diagnosis of child abuse was made by a health care professional at the clinical site; “Probable” indicates that the diagnosis of child abuse was a part of the differential diagnosis of the clinical team but a final diagnosis had not been made; “Possible” indicates that there is documentation within the medical record that child abuse was being considered. The clinical characteristics are reported by age subgroup as means and standard errors for continuous variables and percentages for discrete variables. Analyses of variance were used to test the equality of the means across the group for continuous variable and chi-square tests were used to compare percentages for discrete variables. If significant differences were identified ($p < 0.05$), pairwise post-hoc comparisons were carried out (t-test for continuous variables, chi-square for discrete variables), with a Bonferroni (BF) correction for multiple comparisons ($p < 0.05/3$). Kaplan-Meier curves were generated for each age subgroup describing the time of death of study participants. A log-rank was used to compare the curves. Cox proportional hazards regression models were used to assess the effect of age on time to death while controlling for covariates. Data in all tables are presented as mean (± SEM) unless otherwise noted.

Results

Of the first 200 subjects enrolled in the ADAPT Trial, the 45 subjects (22.5%) with concern for abuse were excluded from this analysis. Of the remaining 155 subjects, 43 children were <5y, 45 children were 5 -<11y and 67 children were 11–<18y (Table 1). There was no difference in proportion of females in the 3 groups (34.9% vs. 40.0% vs. 31.3%, $p = 0.641$). With respect to race, 106 children were white, 31 were black, and 18 were classified as “other” and there was an increased representation of white children in the two oldest cohorts

when compared to the youngest cohort (48.8% vs. 73.3% vs. 76.1%, p = 0.02 overall; p = 0.042 for <5 vs.5-<11y, p = 0.082 for <5y vs. 11-<18y). As expected, the 3 groups differed significantly by weight (14.9 kg ± 0.5 vs. 29.4 kg ± 1.4 vs. 58.5 kg ± 2.1, p < 0.001 overall and across all groups). With respect to the cause of injury, 101 subjects were in motor vehicle collisions, 26 had falls, 4 had homicide/assault and 24 were classified as “other.” There were trends in causes of injury among the different age groups, as the middle group tended to be more likely to be involved in a motor vehicle accident than to sustain a fall, but the trends did not reach statistical significance (p = 0.094). There were no differences in type of injury among the 3 groups but the oldest group was more likely to be under the influence of drugs (0% vs. 0% vs. 8.5%, p = 0.013). There were no differences between the three age groups with respect to transportation to the hospital and there was no difference in GCS scores at the time of ICP monitor placement among the age groups (5.2 ± 0.3 vs. 5.6 ± 0.3 vs. 5.2 ± 0.2, p = 0.64).

The relationship between age, injury characteristics and pre-hospital events is shown in Table 2. The oldest group had increased Head AIS scores compared to the other two groups (4.0 ± 0.2 vs. 4.1 ± 0.1 vs. 4.4 ± 0.1, p = 0.040 overall; p = 0.049 for <5y vs. 11-<18y and p = 0.023 for 5-<11y vs. 11-<18y). The youngest group tended to have more apnea events (20.9% vs. 15.6% vs. 4.5%, p = 0.086) and there were no other differences among age groups with other pre-hospital events assessed.

The impact of age on measures during the resuscitation phase is shown in Table 3. Overall, there was a difference in the incidence of hypothermia between the groups (35.7% vs. 26.7% vs. 12.1%, p = 0.014 overall; p = 0.004 for <5y vs. 5-<11y and p = 0.05 for <5y vs. 11-<18y). Fluids administered (ml/kg/hr) prior to ICP monitor placement was greater in the youngest group compared to the oldest (12.0 ± 1.3 vs. 8.5 ± 1.0), while fluid output was not different. There were several associations between the groups with respect to laboratory values. Compared to the oldest cohort, the youngest cohort had (i) lower hemoglobin concentrations (10.7 g/dl ± 0.3 vs. 11.8 g/dl ± 0.2, p = 0.003), (ii) greater incidence of abnormal PTT (39.5% vs. 19.4%, p = 0.004) and (iii) greater incidence of abnormal INR (27.9% vs. 17.9%, p = 0.005). The older cohort demonstrated lower platelet counts compared to the middle cohort (248×10^3 ± 10.9 vs. 297×10^3 ± 12.0, p = 0.006). Lastly, there were no differences in other events during the resuscitation phase among the age groups.

The association between age and PRISM III variables is shown in Table 4. While age-related differences in heart rate and blood pressures were observed, the highest recorded pH differed across the age strata and was lower in the youngest cohort compared to the oldest cohort (7.40 ± 0.01 vs. 7.44 ± 0.01, p = 0.011). Moreover, the highest blood urea nitrogen (BUN) and creatinine (Cr) varied among the 3 age strata (BUN: 12.6 mg/dl ± 0.6 vs. 14.4 mg/dl ± 0.6 vs. 14.3 mg/dl ± 1.4, p = 0.036 overall, p = 0.03 for <5 vs. 5-<11y and p = 0.019 for <5 vs. 11-<18y; Cr: 0.4 mg/dl ± 0.01 vs. 0.6 mg/dl ± 0.01 vs. 0.8 mg/dl ± 0.01, p < 0.0001 overall and between all groups). The neurologic examination at the time the child qualified for the study is shown in Table 5. Of note, many aspects of the entire examination were not tested for a large proportion of the overall population.

Uncorrected mortality rates of the 3 age groups were not different (14.0% vs. 20.0% vs. 20.9%). Cox proportional hazard ratios [HR, referenced to <5 y] for the middle cohort = 1.469; HR for oldest cohort = 1.544, p = 0.660). After adjusting for potential confounders, the HR for cohorts was not significantly different (HR = 1.407 and 1.192, respectively, p = 0.906).

Discussion

The current evidence-based guidelines for management of severe TBI in children were developed to make recommendations for children across the entire age spectrum and the overall goals of the ADAPT trial are to expand these guidelines for clinicians and researchers. With the exception of cerebral perfusion pressure (CPP) thresholds, none of the guidelines attempt to account for differences in ages of the children who were injured despite the widely held belief that treatment recommendations for infants and teenagers may need to differ (5). However, the existing literature that informs the guidelines are simply insufficient to describe how age affects outcomes after severe TBI in children. We undertook the current study to describe the association between age and mortality and included a number of other variables to try to define characteristics of the various age groups. In this relatively large cohort of 155 children with severe TBI who underwent intracranial monitoring, we did not find a difference in mortality between subjects across 3 age strata that have been previously observed.

The relationship between young age and outcome after neurological insults has a long history in developmental neuroscience. Some suggest that since dendritization, myelination, and synaptogenesis occur early during development, early insults may be better tolerated because of these developmental processes can adapt (20–23). This “early plasticity theory” would suggest younger animals may have improved outcomes after an injury. On the contrary, others argue that an injury during this developmental stage may lead to a more vulnerable brain as these developmental processes are disrupted (24–29). As these developmental processes continue over many years, we chose to study mortality in our large cohort study to start to identify factors that might have an impact on this more immediate outcome.

To date, our study represents one of the larger cohorts to interrogate the relationship between age and mortality in children with severe TBI. Levin studied 103 children with severe TBI and found that children < 4 y had the highest mortality (almost 80% at 1 year after injury) and children 5–10 y had the lowest (~20%)(12). However, they did not control for covariates and likely included children with abusive head trauma, in contrast to our work. Their high mortality rates in the youngest cohort could be explained because this cohort (i) had lower GCS scores, (ii) worse pupillary exam, (iii) more surgically-evacuated lesions, (iv) increased shock, and (v) higher ICPs. Similarly, Michaud reported that mortality was highest in children < 2 y (50%) compared to older children (35% for 3–14y; 14% for > 14y)(19). In regression analysis, they found injury severity scores and pupillary exam were the most significant predictors of mortality. In contrast to these studies, we found no differences in mortality across similar age strata, with the youngest cohort exhibiting a non-significant trend toward lower mortality. In a very large cohort, Morrison and colleagues

analyzed 16,000 children in the National Pediatric Trauma Registry and showed a higher mortality in the pre-pubertal group (0 – 7y) while controlling for other contributing factors (30). However, this study included mild/moderate/severe TBI children with a concomitantly low mortality rate (5%). Most consistent with our findings, Berger and colleagues found a non-significant trend of decreased mortality in children < 5y compared to those 6 – 10y and 11 – 17y (25% vs. 42.8% vs. 35.7%) in 37 children (13).

Of interest, two large, French studies have addressed the relationship between age and other characteristics with outcomes. In the first report, Ducrocq and colleagues interrogated a trauma registry to determine early predictive factors associated with outcome in children with TBI (10). The investigators state that the children (n = 585) all had severe TBI – yet the median GCS was 6 with an interquartile ratio from 3 – 8 – indicating at least some of the subjects might have had a post-resuscitation GCS > 8. Nevertheless, analysis of this large cohort indicated that age < 2 y was associated with increased mortality independent of other risk factors. Similarly, Tude Melo and colleagues studied 315 children from the same Parisian trauma center over a 6-year period (11). In this series, mortality rate was quite high (30%) and the investigators found that age < 2 and other factors (initial GCS score [≤ 5], accidental hypothermia, hyperglycemia and coagulation disorders) were independent risk factors for mortality. While they found that children < 2 y of age had a very high mortality rate (47%) despite resuscitation and transportation to the hospital by highly trained personnel. Neither report indicated whether child abuse was suspected in this young cohort – thereby making direct comparison with our data difficult.

To put our association between age and mortality into context with these other studies, the differences between studies is likely due to differences in inclusion/exclusion criteria (the requirement for placement of an ICP monitor and the exclusion of AHT children), clinical practice differences over different time epochs as neurotrauma care has improved and the ability of studies to use statistical adjustments for measured co-variates. An important consideration in comparing our work to previous studies is the decision to include or exclude children with abusive head trauma. Results from several studies show worse outcome in abusive head trauma (AHT), although many were limited by the same factors of other papers related to age: limited sample size (implying limited statistical power to detect differences) and other study design flaws such as selection bias related to patient recruitment (16–18, 31). Since AHT are undoubtedly part of the youngest cohort in any analysis, this would obviously lead to worse outcomes in this youngest group (32). To avoid these pitfalls and to more fully explore the epidemiology age in children with severe TBI without being overwhelmed by the effect of AHT, we did not include abuse in this analysis. Interestingly, even after excluding children with AHT – a condition whereby caregivers often refuse to seek medical care in a timely manner - we still detected differences in hospital transport across the age strata.

Within our comprehensive assessments of this cohort, we found associations between age and the various factors that could be potential hypotheses for the field to explore. Some of these associations are quite expected – weight, heart rates, blood pressure and measures of renal function differ by age – but still emphasize that clinicians caring for children across the entire age range will need to account for these factors. Other associations were

quite novel and could impact care and outcomes. For example, the youngest children were more likely to have presented with hypothermia during the resuscitation phase compared to older children. This may be due to developmental differences in temperature regulation during resuscitation, differences in injury severity or a result of exposure in infants with increased surface area:volume. The impact of spontaneous hypothermia early after injury is uncertain, despite several RCTs attempting to study it's effects (33–35). We detected associations between hematopoetic system and age, with younger subjects demonstrating alterations in hemoglobin, PTT and INR and the oldest children demonstrating lower platelet counts. These findings need to be explored to establish why these associations manifest in the different age groups.

There are limitations to our study. The most important is the possibility of a Type 2 error, concluding that age and mortality are unrelated when an association actually exists. Because this analysis represents one of the larger cohorts to date, this concern is somewhat mitigated and we expect that an analysis of the full cohort of 1000 children may be more illustrative. It is also possible that medical decisions, such as those related to withdrawal of life support, could also be influenced by the age of the child. Our completed study will assess outcomes based on Glasgow Outcome Scale-Extended for Pediatrics, which may assist us in understanding the extent of this limitation. Our study is necessarily biased toward children who meet our inclusion criteria - with ICP monitoring being required to be a part of this study. It is possible that there is an inherent bias within the sites where ICP monitoring is more or less likely to occur. Unfortunately, there is no way for us to know how this bias influences our results. As a corollary to this limitation, children who were deemed too severely injured to benefit from ICP monitoring – thereby underestimating the mortality of overall TBI in the broader population at the clinical sites. Because our overall study design of ADAPT was to determine the effectiveness of ICP-derived therapies (among others), we believe that our choice for inclusion/exclusion were warranted despite this potential bias for this study. Lastly, we did not account for premorbid conditions for this analysis as has been done by others (36–37). We do anticipate performing this type of analysis on the larger cohort when all outcome information is available to us.

In conclusion, we failed to detect differences in mortality in children of differing ages with severe TBI as others have in the past. We have also found several provocative associations that will need to be confirmed in larger cohorts and other populations of children. We feel that the work of understanding how age affects outcomes – including secondary injury characteristics, mortality and eventually functional outcomes – is essential to understand the natural history of the disease. It is only with analyses such as ours that we can advance toward a more patient-centered approach to care for children across the entire age range.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Demographic and Injury Characteristics by Age of Child.

Variables	Total	Age (in years)			*p* [a]	Pairwise comparisons		
		<5 N=43	5–<11 N=45	11–<18 N=67		A v B	A v C	B v C
Age, mean years	9.2 (0.4)	3.0 (0.2)	7.9 (0.2)	14.1 (0.2)	<.001	<.001[b]	<.001[b]	<.001[b]
Sex, *n* (%)					0.641			
Female	54 (34.8)	15(34.9)	18(40.0)	21 (31.3)				
Male	101 (65.2)	28(65.1)	27 (60.0)	46 (68.7)				
Race, *n* (%)					0.020	0.042	0.008[b]	0.618
White	106 (68.4)	21 (48.8)	33 (73.3)	52 (77.6)				
Black	31 (20.0)	13 (30.2)	9 (20.0)	9(13.4)				
Other	18(11.6)	9 (20.9)	3(6.7)	6(9.0)				
Weight (in kg)	37.8 (1.8)	14.9(0.5)	29.4(1.4)	58.5(2.1)	<.001	<.001[b]	<.001[b]	<.001[b]
Primary language, *n (%)*					0.728			
English	135 (88.2)	38(90.5)	38 (84.4)	59 (89.4)				
Spanish	13(8.5)	4(9.5)	5(11.1)	4(6.1)				
Sign	1 (0.7)	0(0.0)	0(0.0)	1(1.5)				
Other	4(2.6)	0(0.0)	2(4.4)	2(3.0)				
Cause of injury, *n* (%)					0.094			
Motor vehicle	101 (65.2)	28(65.1)	32(71.1)	41 (61.2)				
Accidental fall	26(16.8)	12 (27.9)	4 (8.9)	10(14.9)				
Homicide/assault	4(2.6)	0 (0.0)	2(4.4)	2(3.0)				
Other	24(15.5)	3(7.0)	7(15.6)	14 (20.9)				
Type of injury, *n* (%)					0.989			
Closed	133 (85.8)	37 (86.0)	38 (84.4)	58 (86.6)				
Penetrating	14(9.0)	4(9.3)	5(11.1)	5(7.5)				
Blast	1 (O.b)	U (U.O)	0 (0.0)	1(1.5)				
Crush	7(4.5)	2(4.7)	2(4.4)	3(4.5)				
Mechanism of injury, *n* (%)					0.804			
Acceleration/Deceleration	15(9.7)	3(7.1)	7(15.6)	5(7.5)				
Direct impact/Fall	120(77.9)	34(81.0)	33 (73.3)	53(79.1)				
Penetrating	12 (7.8)	3(7.1)	4(8.9)	5(7.5)				
Other	7(4.5)	2(4.8)	1 (2.2)	4(6.0)				
Likelihood under the influence, *n*(%)					0.013	0.618	0.072	0.068
None	142 (96.6)	43(100)	45(100)	54(91.5)				
Confirmed	5(3.4)	0(0.0)	0(0.0)	5(8.5)				
Transported to study hospital from, *n* (%)					0.516			
Scene of injury	101 (65.2)	29 (67.4)	31 (68.9)	41 (61.2)				
Home	52 (33.5)	13(30.2)	13(28.9)	26 (38.8)				
Other hospital	2(1.3)	1 (2.3)	1 (2.2)	0(0.0)				
Glasgow coma scale	5.3(0.1)	5.2 (0.3)	5.6(0.3)	5.2 (0.2)	0.640			

NA = not applicable.

[a] Kruskal-Wallis chi-square test or Pearson's chi-square test for continuous or categorical variables, respectively.

[b] Significant after Bonferroni correction.

TABLE 2.

Injury and Pre-Hospital Characteristics by Age of Child

Variables	Total	Age (in years)			*P* [a]	Pairwise comparisons		
		<5 N=43	5–<11 N=45	11–<18 M=67		A v B	A v C	B v C
Abbreviated Injury Score								
Head	4.2(0.1)	4.0 (0.2)	4.1 (0.1)	4.4(0.1)	0.040	0.759	0.049	0.023
Face	1.0(0.1)	1.1 (0.2)	1.0(0.2)	1.1(0.1)	0.560			
Neck	0.2(0.1)	0.1 (0.1)	0.1 (0.1)	0.4(0.1)	0.296			
Thorax	1.1(0.1)	1.3 (0.3)	1.2(0.2)	1.0(0.2)	0.838			
Abdomen	0.6(0.1)	0.7 (0.2)	0.5 (0.2)	0.5(0.1)	0.609			
Spine	0.5(0.1)	0.7 (0.2)	0.4(0.2)	0.3(0.1)	0.081			
Upper extremities	0.5(0.1)	0.6 (0.2)	0.5(0.1)	0.5(0.1)	0.955			
Lower extremities	0.7(0.1)	0.5 (0.2)	0.8(0.2)	0.8(0.1)	0.155			
External	0.6(0.1)	0.8(0.2)	0.7(0.1)	0.4(0.1)	0.243			
Injury Severity Score	28.4(1.0)	29.4 (2.4)	28.0 (2.0)	27.9(1.3)	0.908			
Pre-hospital events, *n (%)*								
Apnea					0.086			
Yes	19(12.3)	9(20.9)	7(15.6)	3(4.5)				
No/Unknown	126(81.3)	32 (74.4)	35 (77.8)	59(88.1)				
Suspected	10(6.5)	2(4.7)	3(6.7)	5(7.5)				
Aspiration					0.859			
Yes	3(1.9)	1 (2.3)	1 (2.2)	1(1.5)				
No/Unknown	128(82.6)	34(79.1)	39 (86.7)	55(82.1)				
Suspected	24(15.5)	8(18.6)	5(11.1)	11(16.4)				
Cardiac arrest					0.316			
Yes	14(9.0)	6(14.0)	5(11.1)	3(4.5)				
No/Unknown	138(89.0)	37 (86.0)	39 (86.7)	62(92.5)				
Suspected	3(1.9)	0(0.0)	1 (2.2)	2(3.0)				
Hypotension					0.217			
Yes	24(15.5)	7(16.3)	11(24.4)	6(9.0)				
No/Unknown	125 (80.6)	35(81.4)	32(71.1)	58(86.6)				
Suspected	6(3.9)	1 (2.3)	2(4.4)	3(4.5)				
Hypoxia					0.735			
Yes	11(7.1)	2(4.7)	3(6.7)	6(9.0)				
No/Unknown	126(81.3)	38(88.4)	36 (80.0)	52 (77.6)				
Suspected	18(11.6)	3(7.0)	6(13.3)	9(13.4)				
Seizure					0.814			
Yes	12(7.7)	5(11.6)	2(4.4)	5(7.5)				
No/Unknown	132 (85.2)	35(81.4)	40 (88.9)	57(85.1)				
Suspected	11(7.1)	3(7.0)	3(6.7)	5(7.5)				
Hypothermia					0.501			
Yes	10(6.5)	4(9.3)	3(6.7)	3(4.5)				

Variables	Total	Age (in years)			*p* [a]	Pairwise comparisons		
		<5 N=43	5–<11 N=45	11–<18 M=67		A v B	A v C	B v C
No/Unknown	136 (87.7)	36 (83.7)	38(84.4)	62(92.5)				
Suspected	9(5.8)	3(7.0)	4(8.9)	2(3.0)				
Hyperventilation					1.000			
Yes	4(2.6)	1 (2.3)	1 (2.2)	2(3.0)				
No/Unknown	150(96.8)	42 (97.7)	44 (97.8)	64(95.5)				
Suspected	1 (0.6)	0 (0.0)	0(0.0)	1(1.5)				

For this analysis, prehospital events are defined as events that occurred after injury but before arrival at the study hospital.

NA = not applicable.

[a] Kruskal-Wallis chi-square test or Pearson's chi-square test for continuous or categorical variables, respectively.

[b] No comparison significant after Bonferroni correction

TABLE 3.

Resuscitation Measures by Age of Child

Variables	Total	Age (in years)			*P* [a]	Pairwise compairisons		
		<5 N=43	5–<11 N=45	11–<18 N=67		A v B	A v C	B v C
Complications, *n* (%)								
Cardiac arrest	7(4.5)	2(4.7)	3(6.7)	2(3.0)	0.63			
Hypotension	45(29.0)	12(27.9)	16(35.6)	17(25.4)	0.49			
Hypoxia	5(3.2)	2(4.7)	2(4.4)	1(1.5)	0.601			
Seizure	15(9.7)	6(14.0)	5(11.1)	4(6.0)	0.357			
Hyperthermia	19(12.4)	3(7.1)	4(8.9)	12(18.2)	0.165			
Hypothermia	35(22.9)	15(35.7)	12(26.7)	8(12.1)	0.014	0.362	0.004[b]	0.050
Hyperventilation	34 (22.2)	8(19.0)	10(22.2)	16(24.2)	0.818			
Medications, *n (%)*								
Anticonvulsant	57(36.8)	15(34.9)	15(33.3)	27 (40.3)	0.721			
Hypertonic saline	61 (39.4)	16 (37.2)	18(40.0)	27 (40.3)	0.944			
Mannitol	36 (23.2)	11(25.6)	8(17.8)	17(25.4)	0.590			
Barbiturate	6(3.9)	1 (2.3)	2(4.4)	3(4.5)	1.000			
Fluids, ml/kg/hr								
In	9.9 (0.7)	12.0(1.3)	9.9(1.3)	8.5(1.0)	0.043	0.126	0.016[b]	0.296
Out	4.0(0.4)	4.1 (0.9)	3.4(0.8)	4.2 (0.6)	0.322			
Labs								
Hemoglobin (g/dl)	11.3(0.2)	10.7 (0.3)	11.2(0.2)	11.8(0.2)	0.005	0.158	0.003[b]	0.069
Platelets (103/ml)	268(7.5)	270(16.5)	297(12.0)	248(10.9)	0.022	0.186	0.249	0.004[b]
White blood cell (10^3ml)	17.6(0.6)	16.6(1.0)	18.0(1.2)	17.9 (0.9)	0.618			
Sodium (meq/L)	141 (0.4)	141 (0.9)	141 (0.6)	141 (0.7)	0.969			
PT (sec)					0.177			
≥15	61 (39.4)	21 (48.8)	14(31.1)	26 (38.8)				
<15	66(42.6)	12(27.9)	22 (48.9)	32 (47.8)				
Unknown/NA	28(18.1)	10(23.3)	9(20.0)	9(13.4)				
PTT (sec)					0.021	0.301	0.004[b]	0.184
≥32	42(27.1)	17(39.5)	12(26.7)	13(19.4)				
<32	90(58.1)	17(39.5)	25(55.6)	48(71.6)				
Unknown/NA	23(14.8)	9(20.9)	8(17.8)	6(9.0)				
INR					0.025	0.151	0.005[b]	0.243
≥1.5	31 (20.0)	12(27.9)	7(15.6)	12(17.9)				
<1.5	97(62.6)	19 (44.2)	29 (64.4)	49(73.1)				
Unknown/NA	27(17.4)	12(27.9)	9(20.0)	6(9.0)				
pH					0.321			
≥7.25	93(60.0)	20 (46.5)	29 (64.4)	44 (65.7)				
<7.25	29(18.7)	11(25.6)	8(17.8)	10(14.9)				
Unknown/NA	33(21.3)	12(27.9)	8(17.8)	13(19.4)				

Variables	Total	Age (in years)			P [a]	Pairwise compairisons		
		<5 N=43	5–<11 N=45	11–<18 N=67		A v B	A v C	B v C
PaO_2 (mm Hg)					0.814			
≥60	102(65.8)	29 (67.4)	30 (66.7)	43 (64.2)				
<60	12(7.7)	3(7.0)	5(11.1)	4(6.0)				
Unknown/NA	41 (26.5)	11(25.6)	10(22.2)	20 (29.9)				
pCO_2 (mm Hg)					0.144			
<30	15(9.7)	2(4.7)	2(4.4)	11(16.4)				
≥30	67 (43.2)	15(34.9)	25(55.6)	27 (40.3)				
≥45	41 (26.5)	15(34.9)	10(22.2)	16(23.9)				
Unknown/NA	32 (20.6)	11(25.6)	8(17.8)	13(19.4)				
HCO3 (meq/L)					0.571			
≥18	109(70.3)	26 (60.5)	33(73.3)	50 (74.6)				
<18	15(9.7)	6(14.0)	4(8.9)	5(7.5)				
Unknown/NA	31 (20.0)	11(25.6)	8(17.8)	12(17.9)				

For this analysis, resuscitation phase of care represents events/findings that occurred after arrival at the study hospital but before the ICP monitor was placed.

NA = not applicable.

[a] Fisher's F test or Kruskal-Wallis chi-square test for continuous variables, Pearson's chi-square test or Fisher's exact test for categorical variables.

[b] Significant after Bonferroni correction.

TABLE 4.

PRISM III Variables by Age of Child

Variables	Total	Age (in years)			*P* [a]	Pairwise comparisons		
		<5 N=43	5–<11 N=45	11–<18 N=67		A v B	A v C	B v C
Vital signs								
Lowest systolic BP (mmHg)	84.7(1.6)	75.1 (3.1)	84.1 (2.8)	91.4(2.2)	<.001	0.033	<.001[b]	0.040
Highest heart rate (beats/min)	142(2.5)	156(4.8)	144(4.1)	133 (3.7)	<.001	0.066	<.001[b]	0.039
Highest temperature (°C)	37.9(0.1)	38.0(0.1)	37.6 (0.2)	38.0(0.1)	0.751			
Lowest temperature (°C)	35.2(0.1)	34.9 (0.3)	34.9 (0.3)	35.6 (0.2)	0.199			
Mental status								
Lowest GCS (no paralysis)	4.8(0.2)	4.4 (0.3)	4.9 (0.3)	5.1 (0.3)	0.239			
Pupillary reflexes, *n (%)*					0.890			
Both reactive	103(67.8)	27 (65.9)	29 (64.4)	47(71.2)				
One fixed, one reactive	14(9.2)	3 (7.3)	5(11.1)	6(9.1)				
Both fixed	35(23.0)	11(26.8)	11(24.4)	13(19.7)				
Blood Gases								
Highest pH (mmol/L)	7.4(0.01)	7.4 (0.01)	7.4 (0.01)	7.4 (0.01)	0.038	0.092	0.01 1[b]	0.471
Highest total CO2 (mmol/L)	18.0(0.9)	18.5(1.5)	20.1 (1.4)	16.3(1.5)	0.398			
Lowest PaO2 (mmHg)	132(5.7)	132(8.5)	121(10.0)	138(9.8)	0.526			
Lowest pH (mmol/L)					0.218			
≥7.25	104(67.1)	24(55.8)	29 (64.4)	51 (76.1)				
<7.25	43(27.7)	16(37.2)	13(28.9)	14(20.9)				
Unknown/NA	8(5.2)	3(7.0)	3(6.7)	2(3.0)				
Lowest total CO2 (mmol/L)					0.154			
<30	125(80.6)	37 (86.0)	37 (82.2)	51 (76.1)				
≥30	2(1.3)	0(0.0)	2(4.4)	0(0.0)				
Unknown/NA	28(18.1)	6(14.0)	6(13.3)	16(23.9)				
Highest pCO2 (mmHg)					0.603			
≥45	55(35.5)	18(41.9)	15(33.3)	22 (32.8)				
<45	92(59.4)	22(51.2)	27 (60.0)	43 (64.2)				
Unknown/NA	8(5.2)	3(7.0)	3(6.7)	2(3.0)				
Chemistries								
Highest glucose (mg/dL)	197(6.0)	211(12.9)	200(12.1)	187 (7.7)	0.558			
Highest potassium (mmol/L)	4.1(0.1)	4.1 (0.1)	4.0(0.1)	4.2(0.1)	0.373			
Highest blood urea nitrogen (mg/dL)	13.9(0.6)	12.6(0.6)	14.4(0.6)	14.3(1.4)	0.036	0.030	0.941	0.019
Highest creatinine (mg/dL)	0.62 (0.02)	0.42 (0.02)	0.56 (0.02)	0.78 (0.03)	<.001	<.001[b]	<.001[b]	<.001[b]
Hematology								
Lowest WBC ($\times 10^3/\mu L$)	12.6(0.5)	11.3(0.8)	13.0(1.2)	13.1 (0.6)	0.295			
Lowest platelets ($\times 10^3/\mu L$)	191 (7.0)	179(13.6)	208(12.4)	186(10.7)	0.278			
Hematology, *n* (%)								
Highest PT (in seconds)					0.511			

Variables	Total	Age (in years)			p^a	Pairwise comparisons		
		<5 N=43	5–<11 N=45	11–<18 N=67		A v B	A v C	B v C
≥15	79(51.0)	26 (60.5)	22 (48.9)	31 (46.3)				
<15	61 (39.4)	15(34.9)	17 (37.8)	29 (43.3)				
Unknown/NA	15(9.7)	2(4.7)	6(13.3)	7(10.4)				
Highest PTT (in seconds)					0.231			
≥32	63 (40.6)	23(53.5)	19(42.2)	21(31.3)				
<32	83(53.5)	18(41.9)	23(51.1)	42 (62.7)				
Unknown/NA	9(5.8)	2(4.7)	3(6.7)	4(6.0)				
PRISM III score	17.2(0.8)	18.2(1.8)	17.1(1.3)	16.6(1.0)	0.923			

For this analysis, PRISM III variables were collected in the first 12 hours after injury and recorded.

NA = not applicable.

[a]Fisher's F test or Kruskal-Wallis chi-square test for continuous variables, Pearson's chi-square test or Fisher's exact test for categorical variables.

[b]Significant after Bonferroni correction.

TABLE 5.

Neurological Characteristics by Age of Child

Variables	Total	Age (in years)			*P* [a]	Pairwise compairisons		
		<5 N=43	5–<11 N=45	11–<18 N=67		A v B	A v C	B v C
Status, *n* (%)								
Paralyzed	14(9.1)	5(11.6)	4(9.1)	5(7.5)	0.760			
Sedated	98(64.1)	24(55.8)	34(79.1)	40 (59.7)	0.049	0.021	0.687	0.035
Intubated	126(81.8)	32 (74.4)	38 (86.4)	56 (83.6)	0.311			
Pupil(s) fixed, *n* (%)					0.810			
Both	29(18.7)	6(14.0)	10(22.2)	13(19.4)				
Either	16(10.3)	4(9.3)	6(13.3)	6(9.0)				
Neither	101 (65.2)	30 (69.8)	28(62.2)	43 (64.2)				
Unable to assess/unknown	9(5.8)	3(7.0)	1(2.2)	5(7.5)				
Gaze, *n* (%)					0.086			
Normal	3(1.9)	2(4.7)	1 (2.2)	0(0.0)				
Abnormal	14(9.0)	6(14.0)	5(11.1)	3(4.5)				
Not tested	114(73.5)	30 (69.8)	33 (73.3)	51 (76.1)				
Paralyzed	14(9.0)	5(11.6)	4(8.9)	5(7.5)				
NA	10(6.5)	0(0.0)	2(4.4)	8(11.9)				
Corneal, *n* (%)					0.080			
Normal	20(12.9)	6(14.0)	8(17.8)	6(9.0)				
Abnormal	19(12.3)	4(9.3)	2(4.4)	13(19.4)				
Not tested	91 (58.7)	28(65.1)	28(62.2)	35(52.2)				
Paralyzed	14(9.0)	5(11.6)	4(8.9)	5(7.5)				
NA	11(7.1)	0(0.0)	3(6.7)	8(11.9)				
Cough, *n* (%)					0.025	0.444	0.006[b]	0.182
Normal	27(17.4)	3(7.0)	7(15.6)	17(25.4)				
Abnormal	23(14.8)	6(14.0)	9(20.0)	8(11.9)				
Not tested	82 (52.9)	29 (67.4)	24(53.3)	29(43.3)				
Paralyzed	14(9.0)	5(11.6)	4(8.9)	5(7.5)				
NA	9(5.8)	0(0.0)	1 (2.2)	8(11.9)				
Gag, *n* (%)					0.024	0.138	0.004[b]	0.343
Normal	19(12.3)	1 (2.3)	6(13.3)	12(17.9)				
Abnormal	26(16.8)	6(14.0)	10(22.2)	10(14.9)				
Not tested	87(56.1)	31(72.1)	24(53.3)	32 (47.8)				
Paralyzed	14(9.0)	5(11.6)	4(8.9)	5(7.5)				
NA	9(5.8)	0 (0.0)	1 (2.2)	8(11.9)				
Swallow, *n* (%)					0.116			
Normal	2(1.3)	0 (0.0)	1 (2.2)	1(1.5)				
Not tested	130(83.9)	38(88.4)	39(86.7)	53(79.1)				
Paralyzed	14(9.0)	5(11.6)	4(8.9)	5(7.5)				
NA	9(5.8)	0(0.0)	1 (2.2)	8(11.9)				

A = not applicable.

[a] Pearson's chi-square test or Fisher's exact test.

[b] Significant after Bonferroni correction.