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Survival and Functional Outcome in Children with Traumatic Brain Injury Requiring Ventilatory Support: A Prospective Observational Pilot Study

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Abstract

Background In children, incidence of traumatic brain injury is high and identifying predictors of poor outcome can help clinicians make decisions in the acute phase of treatment. We thus planned to analyze the survival and functional outcome of children following traumatic brain injury. Our study included children (1–10 years of age) requiring ventilation and admitted to trauma intensive care unit of our hospital following traumatic brain injury. Our primary aim was to determine patient outcome using the modified Glasgow Outcome Scale at 3 months following hospital discharge. Our secondary objectives included patient outcome at 1 month following discharge and factors which may affect outcome.

Methods Data (epidemiological, clinical, radiological data, and hospital course) of possible factors affecting survival and outcome of pediatric traumatic brain injury patients were collected. Patient outcome was determined using the modified Rankin Scale at the time of hospital discharge and modified Glasgow Outcome Scale at 1and 3 months following discharge.

Results At the time of hospital admission, 60% children had a Glasgow Coma Scale score of 3 to 8, and were admitted with severe head injury. At the time of discharge, 30% children had good functional outcome, with 50 and 58% children being functionally independent at 1 and 3 months following discharge, respectively. Deranged serum sodium level was an independent predictor of poor neurological outcome on multivariate analysis (coefficient: −3.90 [−5.14 to −2.66, $p < 0.001$]).

Conclusion Fifty-eight percent children, who were admitted to intensive care unit for mechanical ventilatory support, were functionally independent at the end of 3 months following discharge from the hospital, with modified Glasgow Outcome Scale score of 5 or "Normal." Deranged electrolytes result in secondary brain injury, thus contributing to poor long-term outcome. Effective electrolyte management is essential to improve outcome after traumatic brain injury in children.

Keywords
- functional outcome
- pediatric
- survival
- traumatic brain injury

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Introduction

Traumatic brain injury (TBI) is one of the leading causes of admission to pediatric emergencies.[1] Globally, the burden of TBI in children is high, with mortality rates of 29 to 36%.[2,3] Further, children who survive may have lifelong impairment of physical, cognitive, and psychosocial functioning.[3] The incidence and mechanism of TBI differ across various age groups. Some of the major causes of pediatric TBI include fall from height, motor vehicle accidents, and accidental injuries.[4] In a large number of these children, prolonged intensive care treatment and rehabilitation are often required, even in the face of uncertain outcome.[1]

Outcome following TBI may be determined by a number of factors, including age, presence of co-morbidities, mode of injury, and secondary insults in initial days after injury.[1] Despite a high incidence of TBI and its precarious developmental status in young children,[5] most of the parameters by which children with TBI are evaluated are derived from literature and protocols on the adult population. Furthermore, most of the data on the recovery and outcome of pediatric TBI are from the developed world, with there being a paucity of this data from a developing country like ours.

Previous studies on pediatric TBI have identified a high variance in individual outcomes.[1] This may be partly due to the dynamic nature of the nervous system in children and perhaps due to limitations in the ability to quantify the complexity of injury and to determine its impact on neurological development.[5,6] Although standards for clinical care have been published, the scientific basis for these or variant practices is extremely limited. Therefore, in view of the paucity of literature and inadequate data, further research needs to be taken up, so as to evaluate, plan, and transform health care and address the needs of these children. Since evaluating outcome and identifying predictors of poor outcome can help clinicians in making decisions in the acute phase of treatment, we planned to analyze the survival and functional outcome of children admitted to the trauma intensive care unit (ICU) of our hospital for ventilatory support and further management following TBI. The primary aim of our study was to determine patient outcome using the modified Glasgow Outcome Scale (GOS) at 3 months following hospital discharge. Our secondary objectives were to characterize the factors which may affect outcome, modified Rankin Scale (mRS) at the time of hospital discharge, modified GOS at 1 month following discharge, total ventilator days, in-hospital mortality, and length of stay in the ICU and hospital.

Materials and Methods

This prospective observational study was conducted over a period of 1 year (July 2017–July 2018) after obtaining the Institutional Ethics Committee approval and written informed consent from parent/ guardian of children. The study was prospectively registered with the Clinical Trial Registry of India (http://ctri.nic.in; CTRI/2017/12/010972) and included 1 to 10 years old children with TBI, admitted to trauma ICU for ventilatory support and further management. TBI was defined using International Classification of Diseases, 9th revision, code range of 850 to 854 (850: cerebral concussion; 851: cerebral laceration and contusion; 852: subdural, subarachnoid, or extradural hemorrhage; 853: other and unspecified intracranial hemorrhage; 854: intracranial injury and others unspecified).[1] Patients with spinal cord injuries and children whose parents /guardians refused to give consent were excluded from the study.

Data Collection

1) *Epidemiological Data and History*

On admission, the epidemiological data collected included mechanism of injury, method of transport to the hospital, time from injury to hospital admission, resuscitative measures taken, time from hospital admission to ICU admission, time of intubation, history of seizures, associated coillness and injuries.

2) *Clinical Data*

We recorded the Glasgow Coma Scale (GCS) score at the time of hospital admission, severity of head injury (►**Supplementary Table S1**, available in the online version) as per Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013) and Centers for Disease Control and Prevention (2015), pediatric trauma score (PTS).[7] pupillary responses and presence of hypotension (defined as systolic pressure less than 70 mm Hg plus twice the child's age in years[8]) and/or ionotropic support at the time of ICU admission, any complications during ICU stay (including nosocomial infections, meningitis, and septicemia), secondary systemic insults (SSIs), surgical procedures performed, and associated injuries.

3) *Radiological Data*

Computed tomography (CT) scan findings were recorded wherein brain lesions were classified as either diffuse (subarachnoid hemorrhage, brain swelling with edema, and combination of subarachnoid hemorrhage and brain swelling with edema) or focal (epidural, subdural and intracerebral hemorrhage). Ultrasound-guided optic nerve sheath diameter (ONSD) was measured at the time of ICU admission, using a high-frequency (5–10 MHz) ultrasound probe (Sonosite, inc. Bothell. Washington, United States). For each optic nerve, three measurements were made in a transverse plane. The reported ONSD corresponded to a mean of six values obtained for each patient. ONSD value less than 4.5mm was considered normal.[9]

ICU and Hospital Course

On receiving, the patients were assessed for succumbed injuries and airway patency, breathing, circulatory status as well as resuscitative measures were initiated. They were continuously monitored using standard monitors and sedated using intravenous fentanyl (1–2 µg/kg/h) and midazolam (0.5–3.0 µg/kg/min) infusion or intravenous propofol (25–75 µg/kg/min) infusion for 48 hours. They were ventilated using synchronized intermittent mode of ventilation with ventilator parameters set to achieve partial pressure of oxygen of about 100 mm Hg and partial pressure of carbon dioxide in the range of 30 to 35 mm Hg. Children were maintained in head up position and their vitals, pupillary responses, and laboratory parameters were frequently monitored as per individual needs. Children were administered hyperosmolar agents, either intravenous mannitol (0.25–1g/kg, 8 hourly) or 3% NaCl (0.3–0.5 mL/kg/h). Intravenous phenytoin (20 mg/kg followed by 5 mg/kg) was given for 7 days. Those who required prolonged mechanical ventilation were tracheostomized and subsequently weaned off the ventilator. Children were discharged following clinical and radiological improvement, unless other factors that warranted ICU admission were present. Total number of ventilator days, days spent in the ICU/hospital, and in-hospital mortality, if any, were recorded.

During ICU stay, various laboratory parameters, including hemoglobin (Hb <8 gm/dL was considered as a cutoff for blood transfusion), serum sodium levels (normal sodium levels: 135–150 mmol/L, with any two consecutive values beyond the normal range being considered as abnormal), blood sugar (70–200 mg/dL were considered normal), and temperature (normal temperature: 36–38.3 °C) were monitored.

Patient Outcome

Patient outcome was determined using mRS scale[10] at the time of discharge from the hospital. At 1 month and 3 months following hospital discharge, patient outcome was determined using the modified GOS (►**Supplementary Table S2**, available in the online version).[11]

Statistical Analysis

This was a pilot study conducted over a period of 1 year; hence, no formal sample size estimation was done. Statistical analysis was done using SPSS version 22.0. Frequency and percentage were calculated for categorical data. Median (interquartile range [IQR]) was calculated for modified GCS, GOS at 1 month, and GOS at 3 months. Mann–Whitney U test was applied to compare median between two subgroups. Kruskal–Wallis test was applied to compare the median among three subgroups. Spearman's Rank test was applied to find out significant correlation coefficient between lag time for hospital admission, GCS at admission, and PTS versus GOS at 3 months. *p*-Value less than 0.05 was considered statistically significant with 95% confidence interval.

Results

A total of 50 children with TBI, who were admitted to trauma ICU and required ventilatory support, were recruited into the study. The flow of participants in the study is depicted in ►**Fig. 1**. The median age and weight of children included in our study was 4 years (IQR: 2–8years) and 13 kg (IQR: 10–20), respectively. Of the 50 children, 30 (60%) children were boys and 20 (40%) were girls. Fall from height was the most common mode of injury, and majority of the children (60%) were transported by ambulance to the hospital. However, the median time lag from injury to hospital admission was 7 (IQR: 4–18.75) hours and from the time of injury to ICU admission was 26 (IQR: 17.5–36) hours. At the time of hospital admission, 70% of the children required intubation for maintaining their airway with a median time to intubation being 8 (IQR: 4–18.5) hours after injury. The remaining children (30%) were intubated later on during their hospital course. Eventually all of these were admitted in ICU for ventilatory support and management. Majority of the children had no episodes of seizures (66%, 33/50) or any associated comorbidities (96%, 48/50). Of the two children who had associated comorbidities, one had factor VII and the other factor VIII deficiency.

Thirty (60%) children had a GCS score of 3 to 8 at the time of hospital admission, and were admitted with severe head injury. Forty-one (82%) children had a PTS of less than or equal to 8, with 21(42%) of the total children having associated injuries (►**Table 1**). Forty (80%) children with TBI admitted to ICU had high ONSD measurements (ONSD$\geq$0.45cm) on admission. Twenty-nine (58%) children had focal lesions on CT scan (►**Table 1**). Majority ($n = 36$; 72%) of the children admitted to ICU were managed conservatively and had normal electrolytes, temperature, and blood sugar levels. In the ICU, 25 (50%) children suffered SSIs, most commonly respiratory (►**Table 2**). The median mechanical ventilatory days were 6.5 (IQR: 4–10) days. The median ICU and hospital stay was 8.5 (IQR: 5–13) and 10 (IQR: 6–15) days, respectively.

Patients were assessed using mRS score at the time of discharge from the hospital. Twenty-two percent (11/50) children had in-hospital mortality and 40% (20/50) children had either severe (24%, 12/50) or moderately severe (16%, 8/50) disability. Thirty-eight (19/50) percent children had a good functional outcome with mRS grade of either 0, 1 or 2 (►**Fig. 2**). Follow-up evaluations were available for all children who survived till discharge ($n = 39$). Among survivors, six children died within 1 month following discharge. Of the remaining children (33/50), 50% (25/50) were functionally independent with modified GOS score of 5 or "Normal" at 1 month following discharge. At the end of 3 months following discharge, total mortality was 34% (17/50; including 11 patients that had in-hospital mortality and 6 patients that died within 1 month), but more than half of the patients (58%; 29/50) were functionally independent with modified GOS score of 5 or "Normal." About 8% were moderately disabled and functionally dependent (►**Fig. 3**).

►**Table 3** summarizes the regression analysis for the factors affecting patient outcome at 3 months. Univariate analysis showed significant relationship between modified GOS at 3 months and all the predictor variables, namely propofol infusion, PTS, GCS at admission, severity of head injury, serum sodium, and blood sugar. However, multivariate analysis revealed that only serum sodium impacted the patient's outcome at 3 months as assessed by modified GOS. Patients with normal serum sodium had high modified GOS scores at 3 months.

Discussion

TBI is a major cause of disability among children but differs from adults in terms of both pathophysiology and

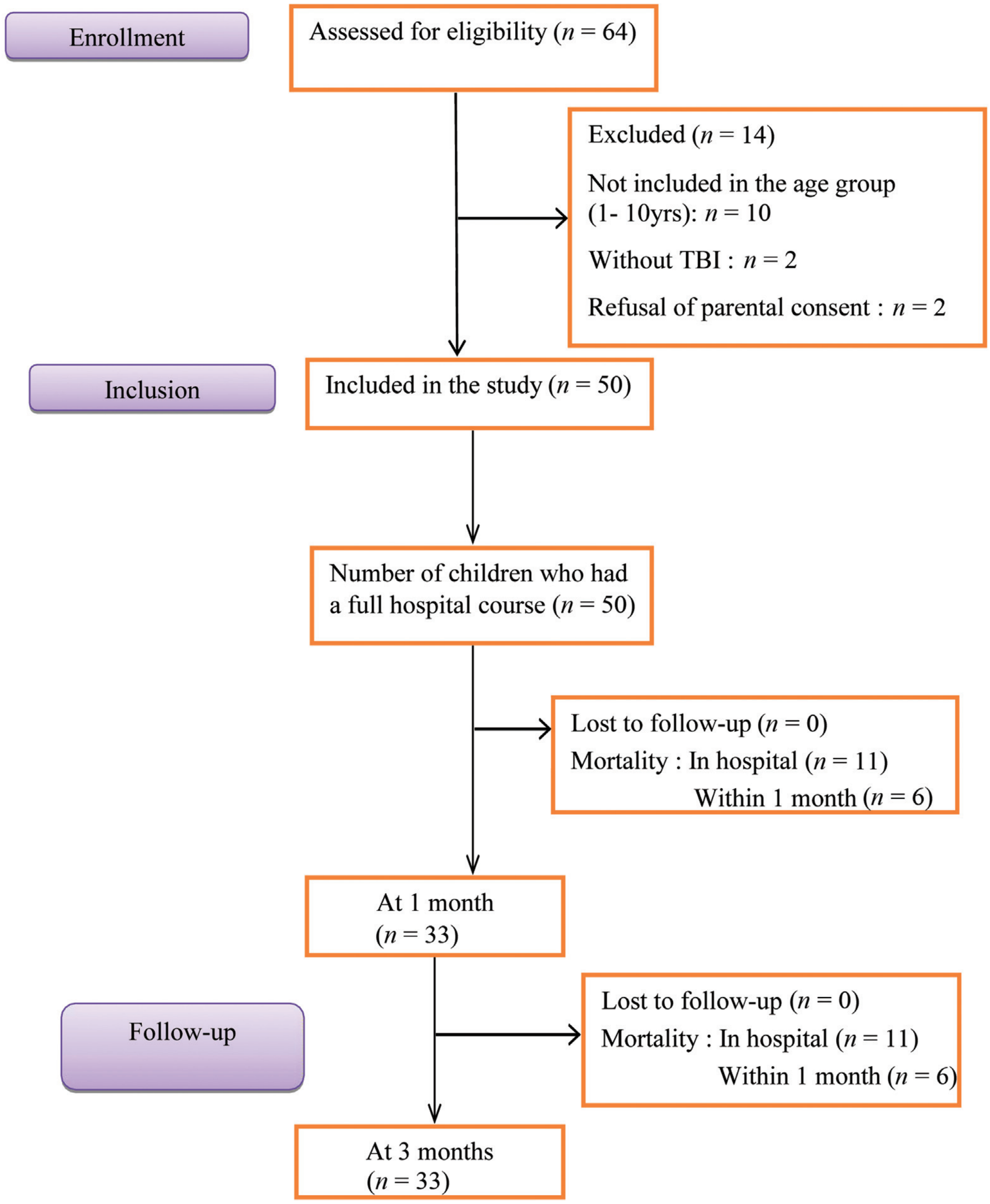

Fig. 1 Consort diagram. TBI, traumatic brain injury.

management.[12,13] These differences can be attributed to age-related structural changes, different mechanisms of injury in children, and challenging neurological evaluation in pediatric population.[13] Further, predicting long-term outcome in children with TBI is difficult and challenging, possibly due to the fact that children go through many different developmental stages.[14] Both parents, as well as clinicians, have to face the burden of uncertainty in predicting long-term outcome. Finding the prognostic factors that can predict outcome in pediatric patients with TBI can greatly help clinicians and intensivists in making decisions in an acute phase of treatment as well as aid in formulating ICU protocols. They can also help in identifying treatable factors leading to secondary brain insults and assist in counseling parents.[14]

In our study, we recruited a total of 50 children admitted with TBI and requiring ventilatory support. Of these, the total in-hospital mortality was 22% (11/50). Clinical status of children at the time of discharge from the hospital is known to have a relation to long-term outcome. Children who were doing well at the time of discharge from the hospital (15/50), continued to do so and had the favorable long-term outcome. Of the 24 children, who were discharged from the hospital with an unfavorable neurological outcome, 14 (58%,14/24) recovered to improve over time with a favorable outcome (modified GOS 5 and normal) at the end of 3 months. Thus, more than half of the patients (58%; 15 + 14 = 29/50) were functionally independent with modified GOS score of 5 or "Normal." Six children died within 1 month of discharge resulting in total mortality of 34% (17 of the total 50 children).

Table 1 Clinical and radiological parameters

Parameters recorded	Number of patients
Hypotension[a]	
At hospital admission	7 (14%)
At ICU admission	9 (18%)
GCS score at the time of hospital admission	
3–8	30 (60%)
9–12	14 (28%)
13–15	6 (12%)
Severity of head injury	
Mild	6 (12%)
Moderate	14 (28%)
Severe	30 (60%)
PTS	
≤8	41 (82%)
> 8	9 (18%)
Pupillary response at the time of ICU admission	
Reactive to light	29 (58%)
Not reactive to light	18 (36%)
Unable to assess	3 (6%)
Associated injuries	
Closed/open fractures	17 (34%)
Major/penetrating injuries	4 (8%)
CT scan findings	
Diffuse lesions	21 (42%)
Focal lesions	29 (58%)
ONSD findings at the time of ICU admission	
< 0.45 cm	10 (20%)
≥0.45 cm	40 (80%)

Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale; ICU, intensive care unit; ONSD, optic nerve sheath diameter; PTS, pediatric trauma score.
Values are expressed as number (percentage).
[a]Hypotension is defined as systolic blood pressure <70 mm Hg+ (age in years × 2).

Table 2 Intensive care unit management

Management parameters	Total number of patients
Management	
Conservative	36 (72%)
Surgical	14 (28%)
Tracheostomy	
Yes	19 (38%)
No	31 (62%)
Hyperosmolar agent used	
None	6 (12%)
IV Mannitol (0.25–1g/kg)	32 (64%)
IV 3% NaCl infusion (0.3–0.5 mL/kg/h)	12 (24%)
Sedation	
IV Propofol infusion (25–75 µg/kg/min)	21 (42%)
IV Fentanyl (1–2 µg/kg/h)—midazolam (0.5–3.0 µg/kg/min) infusion	29 (58%)
Number of patients receiving blood transfusion	9 (18%)
Serum sodium levels	
Normal (135–150mmol/L)	34 (68%)
Abnormal	16 (32%)
Temperature	
Normal (36–38.3 °C)	30 (60%)
Abnormal	20 (40%)
Blood sugar level	
Normal (70–200 mg/dL)	37 (74%)
Abnormal	13 (26%)
Culture	
Positive	15 (30%)
Negative	35(70%)
Secondary systemic insults	
None	25 (50%)
Respiratory	8 (16%)
Circulatory	6 (12%)
Metabolic/electrolytic	7 (14%)
Sepsis	4 (8%)

Abbreviation: IV, intravenous.
Note: All values are expressed as number (percentage).

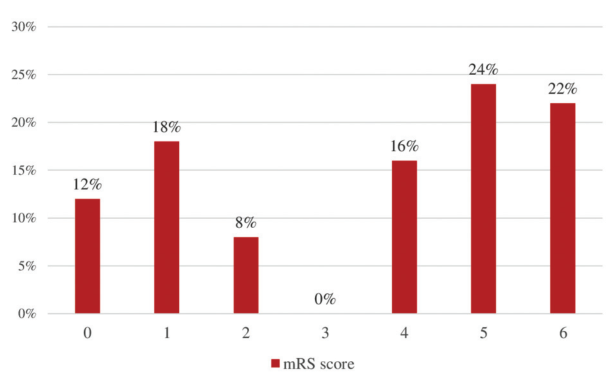

Fig. 2 Modified Rankin Scale (mRS) score on discharge from the hospital.

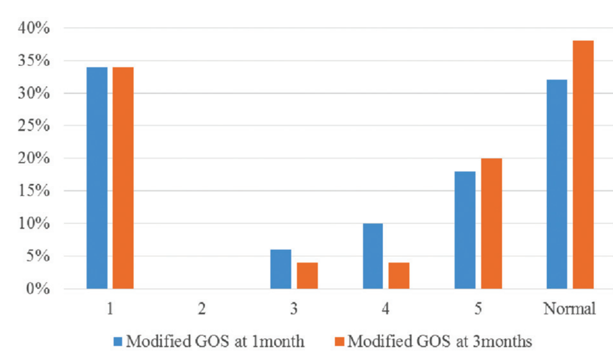

Fig. 3 Modified Glasgow Outcome Scale (GOS) at 1 month and 3 months following discharge.

The median age of children admitted to our ICU was 4 years. Although there are previous reports in literature,[15,16] which claim that within the pediatric population, children less than 5 years have a poorer prognosis, we did not find any significant correlation between age and patient outcome. Nakayama et al[17] in their study also concluded that survival following childhood injury is independent of age groups. Rivara et al[18] had reported that boys had double the rate of head injuries as compared to girls. Consistent with

Table 3 Factors affecting patient outcome-regression analysis for modified GOS at 3 months

Predictor variables	Dependent variable Modified GOS at 3 months Mean (SD)	Coefficient (univariable)	Coefficient (multivariable)
Gender			
Boys	4.4 (2.1)	− 1.25 (−2.50 to −0.00, $p = 0.05^a$)	0.02 (−0.58 to 0.62, $p = 0.96$)
Girls	3.1 (2.3)		
Propofol infusion			
Yes	4.6 (1.9)	3.63 (2.43–4.82, $p < 0.001^a$)	0.04 (−0.98 to 1.06, $p = 0.94$)
No	1.0 (0.0)		
PTS			
≤8	3.6 (2.2)	1.75 (0.17–3.33, $p = 0.03^a$)	0.82 (−0.07 to 1.71, $p = 0.07$)
> 8	5.3 (1.7)		
GCS at hospital admission			
3–8	3.4 (2.2)	1.72 (0.31–3.14, $p = 0.02^a$)	− 0.30 (−1.15 to 0.54, $p = 0.47$)
9–12	5.1 (1.8)	0.81 (−1.10 to 2.72, $p = 0.39^a$)	0.18 (−0.74 to 1.09, $p = 0.70$)
13–15	4.2 (2.5)		
Severity of head injury			
Mild	5.9 (0.4)	−2.52 (−4.41 to −0.64, $p = 0.01^a$)	− 0.99 (−1.89 to −0.09, $p = 0.13$)
Moderate	3.3 (2.3)	−2.10 (−3.90 to −0.29, $p = 0.02^a$)	− 0.63 (−1.49 to 0.23, $p = 0.15$)
Severe	3.8 (2.2)		
Serum sodium			
Normal	5.3 (1.1)	−4.26 (−4.84 to −3.69, $p < 0.001^a$)	− 3.90 (−5.14 to −2.66, $p < 0.001^a$)
Deranged	1.0 (0.0)		
Blood sugar			
Normal	4.9 (1.6)	−3.92 (−4.82 to −3.02, $p < 0.001^a$)	− 0.15 (−1.44 to 1.13, $p = 0.81$)
Deranged	1.0 (0.0)		

Abbreviations: GCS, Glasgow Coma Score, GOS: Glasgow Outcome Scale; PTS, pediatric trauma score; SD, standard deviation.
$^a p < 0.05$, significant.
Note: The "Coefficient (univariable)" column lists the regression coefficient for each of the variables with respect to the dependent variable, when these variables are used as single predictors of the dependent variable, without entering the rest of the variables in the model. The "Coefficient (multivariable)" column lists the coefficients for all the variables when they are entered in the model together (and are now thus controlling for each other); Modified GOS score "normal" is conventionally written as 6.

this finding, in our study also 60% of the children were boys. However, contrary to the findings of Rivara et al, our study showed that boys had better functional outcome than girls following discharge from the hospital. Fall from height was the most common mode of injury in our study population, with road traffic accidents being the second most common cause. These findings were in accordance with those of Garg et al[12] and Dhanda et al[19] wherein the authors reported falls to be the predominant mode of injury in children. However, it is contrary to most Western literature, where road traffic accidents are a more common mode. In our population, especially in lower socioeconomic strata, most of the children are left unattended or in the care of older siblings. Hence, fall from height is a commonly encountered mode of injury. The mode of injury, however, did not affect patient outcome.

Primary injury, which has incurred at the time of trauma, is nontreatable. However, secondary insults like hypoxia and ischemia are treatable and preventable. This is where the prehospital and emergency care comes into play and can have an impact on the long-term patient outcome. Securing the airway at the earliest can remarkably reduce secondary insults. Frequently, the first-aid services are not available at first contact and it is often difficult to find the minimum standard of care at many peripheral centers, subsequently leading to a delay in initiating definite care. In our study, almost all cases were referred from peripheral centers in ambulances, with the median lag time from time of injury to definitive hospital care being almost 7 hours. Majority of the children required intubation on hospital admission for various reasons including poor GCS, raised ICP, hemodynamic instability, or for surgical intervention. However, time from injury to intubation was long (almost 8 hours). This was mainly due to lack of minimum standard of care in most peripheral centers, delay in transporting patients to hospitals, and ill-equipped ambulances with dearth of well-trained pre-hospital emergency care personnel. This could have substantially contributed to increased incidence (50%) of secondary brain insults, thereby negatively impacting prognosis.

Many previous studies[1,20,21] have shown that GCS at the time of hospital admission is an important predictor of prognosis in children admitted with TBI. Majority of the children in our study population presented with GCS of 3 to 8 and were found to have a poor outcome at the end of 3 months (on univariate analysis). PTS used for initial critical assessment was found to have a significant correlation (on univariate analysis) with modified GOS at 3 months, with PTS more than 8 being associated with a better outcome. On multivariate analysis, however, this correlation was not found to be significant. Similarly, Bahloul et al[22] in their study reported a bad outcome in head injured children, presenting with low PTS (3.16 ± 2.1) at the time of hospital admission.

During their ICU stay, two-fifths of the children received propofol for sedation in the initial 48hrs of admission and had a favorable outcome (on univariate analysis) with a median modified GOS of 6 at the end of 3months. On multivariate analysis, however, no significant correlation was found between the use of propofol and outcome at 3months. Though propofol was not used in hemodynamically unstable patients, it can be considered as a sedating agent in hemodynamically stable pediatric TBI patients, in preference to fentanyl and midazolam for initial 48 hours. About 50% children incurred SSIs, with respiratory complications like hypercapnia, hypoxia, hospital-acquired tracheobronchitis, and hospital acquired pneumonia being the most common. This could be due to several reasons. First, there was a huge time lag between the time of injury and time of hospital admission, with the children being intubated on arrival at the hospital. So, there is a possibility that most of the children might have already suffered hypoxic brain insult by the time they reached the hospital. Second, most of the patients were intubated outside the ICU, in the emergency area of our hospital, with a huge lag time (19 hours) between hospital admission and transfer to ICU. As our emergency area has a huge patient inflow, the longer the patients stay in this area, greater are the chances of acquiring hospital infections. Though majority of the children with SSIs had a respiratory pathology, however, it did not significantly impact patient outcome. On the other hand, the presence of electrolyte disturbances, including both hypernatremia and hyponatremia, resulted in an unfavorable patient outcome at 3 months. Serum sodium disturbances were associated with increased mortality; hence, serial serum sodium monitoring is needed while selecting hypertonic saline as osmotic agent. Similarly, in 2013, Alharfi et al[23] claimed that hypernatremia more than 150 mmol/L was an important indicator of mortality. In 2015, Chong et al[24] had shown a significant association between admission hyperglycemia (> 200mg/dL) and poor outcome in children with moderate-to-severe head injury. Likewise in our study, hypoglycemia (<70mg/dL) and hyperglycemia (>200 mg/dL) were associated with significant mortality. However, on multivariate analysis, no significant correlation was found between blood sugar levels and patient outcome at 3 months.

A few limitations of our study were that instead of using an invasive method, which is considered a gold standard for measuring ICP, we used ocular sonography to measure ONSD, which is a noninvasive technique of measuring ICP. Also, children with all grades of severity of head injury were included. Future studies with a larger sample size and similar grades of head injury are required, before the study results can be generalized.

To conclude, more than half of the patients (58%), who were admitted to ICU for mechanical ventilatory support, were functionally independent at the end of 3 months following discharge from the hospital, with modified GOS score of 5 or "Normal." Deranged electrolytes, resulting in secondary brain injury, contributed to poor long-term outcome. Further, children who survive should be efficiently rehabilitated, as many of the children with unfavorable outcomes at discharge from the hospital continue to recover functionally over time.

Conflict of Interest
None declared.

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