Coagulopathy After Isolated Severe Traumatic Brain Injury in Children

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Introduction: Few previous studies have been conducted on the severe traumatic brain injury (sTBI)-associated coagulopathy in children. The purpose of this study was to evaluate the incidence and risk factors of sTBI coagulopathy in a pediatric cohort and to evaluate its impact on outcomes.

Methods: Retrospective analysis of pediatric patients (younger than 18 years) sustaining isolated sTBI [head Abbreviated Injury Scale (AIS) score ≥3 and extracranial injuries AIS score <3]. Criteria for sTBI-associated coagulopathy included thrombocytopenia (platelet count <100,000 per mm^3) and/or elevated international normalized ratio >1.2 and/or prolonged activated partial thromboplastin time >36 seconds. Incidence and risk factors of sTBI coagulopathy and its impact on in-hospital outcomes were analyzed.

Results: Overall, 42.8% (n = 137) of the 320 patients studied developed coagulopathy, with increasing incidence in a stepwise fashion with escalating head AIS score (31.1, 46.2, and 88.6% for head AIS score 3, 4, and 5, respectively; $p < 0.001$). Depressed GCS, increasing age, an ISS ≥16, and brain contusions/lacerations were independently associated with the presence of coagulopathy. The case fatality rate was 7.8% (n = 25); 17.5% versus 0.5% in coagulopathic versus noncoagulopathic patients, respectively. After logistic regression to adjust for confounders, no statistical significant mortality difference in patients with and without coagulopathy was noted (adjusted $p = 0.912$).

Conclusions: Incidence of coagulopathy in children suffering isolated sTBI is exceedingly high at 40% and reflect the head injury severity. A low GCS, increasing age, ISS ≥16 and intraparenchymal lesions proved to be independently associated with TBI coagulopathy.

Key Words: Head injury, Traumatic brain injury, Children, Pediatric, Coagulopathy, Outcome, Risk factor, Mortality.

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Coagulopathy is a well-recognized and frequently observed sequela of severe traumatic brain injury (sTBI) in adults.[1–4] Numerous clinical reports examining adult sTBI cohorts have noted associations between coagulation abnormalities and poor outcomes.[1,5,6] Nevertheless, TBI coagulopathy has not been extensively studied in children. Thus, the aim of this study was to investigate the incidence of and risk factors for coagulopathy in pediatric isolated sTBI patients, to assess its effect on outcomes, and to evaluate the impact of age on the incidence of coagulopathy in these instances.

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METHODS

After Institutional Review Board approval, we retrospectively identified all pediatric isolated sTBI patients (younger than 18 years) admitted to the Los Angeles County + University of Southern California Medical Center Surgical Intensive Care Unit (SICU) from January 2003 through June 2010. Isolated sTBI was defined as a head Abbreviated Injury Scale score (AIS) score ≥3, with chest, abdomen, and extremity AIS score <3.

Demographic and clinical information collected included age, gender, mechanism of injury (blunt vs. penetrating), blood pressure on admission, Glasgow Coma Scale (GCS) score on admission, Injury Severity Score (ISS), AIS for each body region (head, chest, abdomen, and extremity), and type of intracranial injury. All platelet counts, international normalized ratio (INR) values, and activated partial thromboplastin times (aPTT) throughout the SICU stay were accrued.

The pediatric population was stratified into four age groups: infants and toddlers (3 years or younger), preschool age (4–6 years), school age (7–12 years), and adolescents (13–17 years). Hypotension was stratified in age-specific reference points: <60 mm Hg for infants and toddlers, <75 mm Hg for preschool age, <80 mm Hg for school age, and <90 mm Hg for adolescents. The criteria for coagulopathy included thrombocytopenia (platelet count <100,000 per mm^3), INR >1.2, and/or aPTT >36 seconds. Primary outcome for this study was the development of sTBI-associated coagulopathy throughout the SICU stay. Secondary endpoints included ventilator days, SICU, and hospital length of stay (LOS), in addition to in-hospital mortality.

Statistical Analysis

The demographic and clinical characteristics comparing patients with and without coagulopathy were evaluated using bivariate analysis. To further identify the impact of

increasing age on coagulation abnormalities, the incidence of coagulopathy was compared between the stratified age groups. The *p* values for categorical variables were derived from the χ^2 test or two-sided Fisher's exact test, and for continuous variables the Student's *t* test or the Mann-Whitney *U* tests were deployed. Logistic regression was performed to control for confounders diverging significantly ($p < 0.05$) between the compared groups. For continuous outcomes, analysis of covariance was used to adjust for confounders that were significant at $p < 0.05$. To identify risk factors independently associated with the presence of coagulopathy, a stepwise logistic regression was used, and risk factors from the bivariate analysis with a *p* value <0.2 were included into the model.

Values are reported as mean ± standard deviation for continuous variables and as percentages for categorical variables. All analyses were performed using the Statistical Package for Social Sciences (SPSS Windows), version 16.0 (SPSS, Inc., Chicago, IL).

RESULTS

Overall, 320 patients met the inclusion criteria for an isolated sTBI. Of these patients, 281 (87.8%) and 39 (12.2%) were victims of blunt and penetrating trauma, respectively. The overall mean age was 10.7 years ± 5.1 years, and the mean ISS was 15.6 ± 8.8 (Table 1). The predominant injury severity in the cohort was head AIS score 3 (61.2%), followed by head AIS score 4 (25.0%) and head AIS score 5 (13.8%). Specific head injuries of the study group are summarized in Table 2.

Overall, 42.8% (n = 137) developed coagulopathy, 38.4% (n = 108) after blunt and 74.4% (n = 29) after penetrating head injury ($p < 0.001$). In 95.6% (n = 131) of the coagulopathic patients, the diagnosis included an elevated INR, followed by elevated aPTT values in 48.9% (n = 67) and thrombocytopenia in 16.8% (n = 23). With increasing head AIS, the incidence of coagulopathy increased in a stepwise fashion ($p < 0.001$; Fig. 1).

To evaluate the impact of age on the incidence of coagulopathy, the study cohort was subdivided into four age groups as previously described. The rate of male gender and the incidence of penetrating injury mechanism increased significantly with increasing age (Table 3). No statistically significant difference with regard to head injury severity comparing the age groups was found. However, the incidence of coagulation abnormalities increased significantly with advancing age from 26.0% in patients 3 years or younger to 50.7% in adolescents (adjusted $p = 0.012$; adjusted for male

TABLE 1. Demographic and Admission Characteristics in Pediatric Isolated sTBI With and Without Coagulopathy

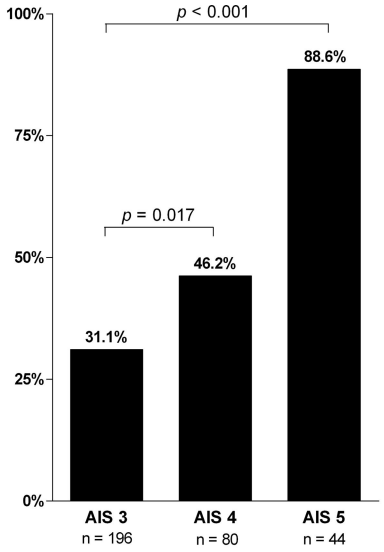
	All Patients (n = 320)	With Coagulopathy (n = 137)	Without Coagulopathy (n = 183)	*p*
Age (yr), mean ± SD	10.7 ± 5.1	11.9 ± 4.8	9.9 ± 5.2	<0.001
Male	73.1% (234/320)	70.1% (96/137)	75.4% (138/183)	0.287
Penetrating MOI	12.2% (39/320)	21.2% (29/137)	5.5% (10/183)	<0.001
GCS score ≤8	22.6% (70/310)	46.2% (61/132)	5.1% (9/178)	<0.001
GCS score 9–12	12.3% (38/310)	13.6% (18/132)	11.2% (20/178)	0.524
GCS score 13–15	65.2% (202/310)	40.2% (53/132)	83.7% (149/178)	<0.001
Hypotension	2.2% (7/314)	4.4% (6/135)	0.6% (1/179)	0.045
ISS, mean ± SD	15.6 ± 8.8	18.9 ± 11.7	13.2 ± 4.4	<0.001
ISS ≥16	41.9% (134/320)	59.1% (81/137)	29.0% (53/183)	<0.001
ISS ≥25	14.4% (46/320)	29.2% (40/137)	3.3% (6/183)	<0.001

SD, standard deviation; MOI, mechanism of injury; GCS, Glasgow Coma Scale; ISS, Injury Severity Score.

TABLE 2. Head Injury Severity and Specific Head Injuries in Pediatric Isolated sTBI With and Without Coagulopathy

	All Patients (n = 320)	With Coagulopathy (n = 137)	Without Coagulopathy (n = 183)	*p*
Head injury severity				
AIS head 3	61.2% (196/320)	44.5% (61/137)	73.8% (135/183)	<0.001
AIS head 4	25.0% (80/320)	27.0% (37/137)	23.5% (43/183)	0.473
AIS head 5	13.8% (44/320)	28.5% (39/137)	2.7% (5/183)	<0.001
Specific head injuries				
Vault fracture	26.9% (86/320)	29.9% (41/137)	24.6% (45/183)	0.287
Base of skull fracture	48.4% (155/320)	43.8% (60/137)	51.9% (95/183)	0.151
EDH	6.9% (22/320)	9.5% (13/137)	4.9% (9/183)	0.110
SDH	12.2% (39/320)	13.9% (19/137)	10.9% (20/183)	0.426
SAH	12.5% (40/320)	12.4% (17/137)	12.6% (23/183)	0.966
EDH/SDH/SAH	36.6% (117/320)	43.1% (59/137)	31.7% (58/183)	0.037
Contusion/laceration	20.0% (64/320)	29.2% (40/137)	13.1% (24/183)	<0.001

EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hemorrhage.



Abbreviations: sTBI, Severe Traumatic Brain Injury; AIS, Abbreviated Injury Scale

Figure 1. Incidence of coagulopathy according to head AIS in pediatric isolated sTBI.

gender, penetrating mechanism of injury, vault fracture, epidural hematoma, and epidural hematoma/subdural hematoma/subarachnoid hemorrhage).

Bivariate analysis was performed to identify risk factors for the presence of coagulopathy (Fig. 2). A stepwise logistic regression analysis identified depressed GCS, increasing age, ISS ≥16, and contusions/lacerations as predisposing risk factors independently associated with the presence of coagulopathy (Table 4). The R^2 for this model was 0.34.

SICU and hospital LOS were significantly prolonged in patients experiencing coagulopathy versus their noncoagulopathic counterparts (Table 5). Figure 3 depicts case fatality rates at observed INR (Fig. 3, A), aPTT (Fig. 3, B), and platelet count (Fig. 3, C) values. The overall case fatality rate was 7.8% (n = 25), 17.5% for coagulopathic and 0.5% for noncoagulopathic patients ($p < 0.001$). However, after logistic regression to adjust for confounders, no statistically significant mortality difference between patients with and without coagulopathy was observed (adjusted $p = 0.91$).

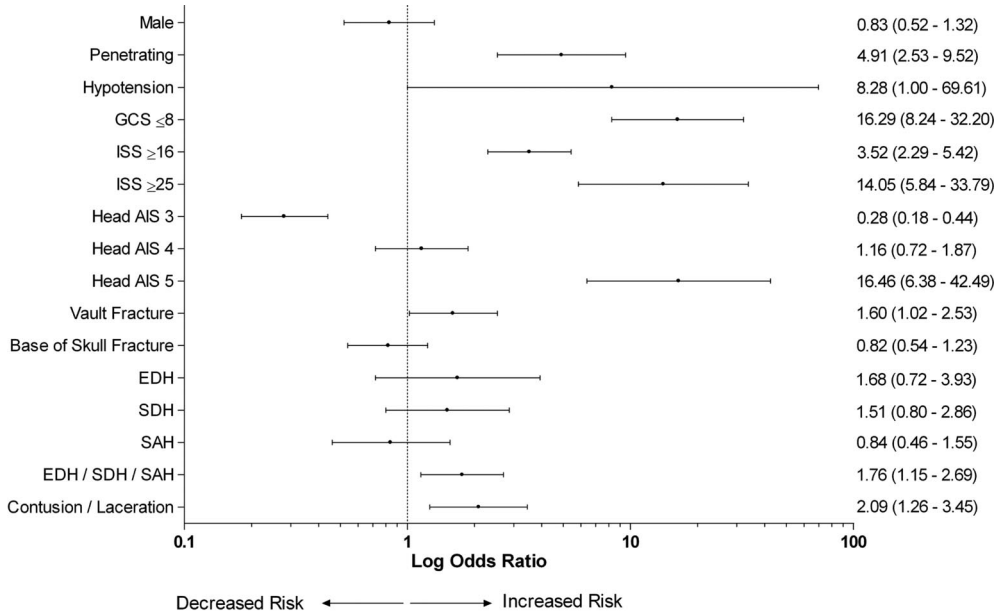
DISCUSSION

The sTBI is frequently associated with marked coagulopathy.[1,2,7] Release of tissue factor after brain injury is conventionally thought to result in an overwhelming activation of the extrinsic coagulation pathway, leading to fibrin deposition and platelet activation that finally results in a consumptive coagulopathy.[2,7,8] The reported incidence of coagulation abnormalities among pediatric sTBI patients is inconsistent and ranges widely from 15% to 87%.[9–16] Chiaretti et al.[9] found an incidence of pathologic admission coagulation disorders in 14.8% of pediatric sTBI patients. Contrary, in a prospective study by Miner et al.,[16] a total of 87% of sTBI patients aged 18 years or younger experienced coagulopathy within 2 hours after head injury. The majority (59%) of the study cohort studied by Miner et al., however, suffered severe concomitant extracranial injuries limiting conclusive associations between TBI and coagulopathy. In our analysis, the overall incidence of coagulopathy throughout the SICU stay was almost 43%, which is comparable with previously published results from our institution observing a coagulopathy incidence of 34% among adult sTBI patients.[1] This range in the reported incidences of coagulopathy in both adult and pediatric sTBI patients likely arises from a variety of factors including the diversity of head injury severities, concomitant extracranial injuries, criteria used to define coagulopathy, and the different times at which coagulation markers were obtained after injury. The seemingly moderate coagulopathy thresholds used in this investigation concur with coagulation abnormalities used in our recent prospective investigation resulting in a significantly increased fatality after severe head injury.[1] Therefore, we believe and demonstrate also in this study that the low-threshold inclusion

TABLE 3. Demographics, Injury Characteristics, and Incidence of Coagulopathy Including Abnormal Coagulation Parameters According to Different Age Groups in Pediatric Isolated sTBI Patients

	All Patients (n = 320)	0–3 yr (n = 50)	4–6 yr (n = 32)	7–12 yr (n = 88)	13–17 yr (n = 150)	p	Adjusted p*
Male	73.1% (234/320)	62.0% (31/50)	59.4% (19/32)	67.0% (59/88)	83.3% (125/150)	0.001	
Penetrating MOI	12.2% (39/320)	10.0% (5/50)	6.2% (2/32)	4.5% (4/88)	18.7% (28/150)	0.008	
GCS score ≤8	22.6% (70/310)	18.4% (9/49)	25.8% (8/31)	22.9% (19/83)	23.1% (34/147)	0.870	
Hypotension	2.2% (7/314)	4.4% (2/45)	0% (0/32)	1.1% (1/88)	2.7% (4/149)	0.500	
ISS, mean ± SD	15.6 ± 8.8	15.9 ± 10.6	14.9 ± 5.7	14.5 ± 5.2	16.4 ± 10.2	0.450	
AIS head 3	61.2% (196/320)	66.0% (33/50)	59.4% (19/32)	67.0% (59/88)	56.7% (85/150)	0.377	
AIS head 4	25.0% (80/320)	20.0% (10/50)	28.1% (9/32)	23.9% (21/88)	26.7% (40/150)	0.773	
AIS head 5	13.8% (44/320)	14.0% (7/50)	12.5% (4/32)	9.1% (8/88)	16.7% (25/150)	0.435	
Coagulopathy	42.8% (137/320)	26.0% (13/50)	43.8% (14/32)	38.6% (34/88)	50.7% (76/150)	0.017	0.012
INR >1.2	40.9% (131/320)	26.0% (13/50)	37.5% (12/32)	36.4% (32/88)	49.3% (74/150)	0.019	0.012
aPTT >36 s	20.9% (67/320)	18.0% (9/50)	28.1% (9/32)	15.9% (14/88)	23.3% (35/150)	0.373	0.549
Platelets <100	7.2% (23/320)	2.0% (1/50)	3.1% (1/32)	6.8% (6/88)	10.0% (15/150)	0.203	0.170

MOI, mechanism of injury; EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hemorrhage.
* Adjusted for male, penetrating MOI, skull fracture, EDH, and EDH/SDH/SAH.



Abbreviations: sTBI, Severe Traumatic Brain Injury; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; EDH, Epidural Hematoma; SAH, Subarachnoid Hemorrhage

Figure 2. Risk factors of sTBI-associated coagulopathy in pediatric patients.

TABLE 4. Independent Risk Factors for Coagulopathy in Pediatric Isolated sTBI

Step	Variable	OR (95% CI)	*p*	R^2
1	GCS score ≤8	12.05 (5.43–26.32)	<0.001	0.287
2	Age group	1.35 (1.04–1.75)	0.027	0.023
3	ISS ≥16	1.88 (1.08–3.28)	0.025	0.017
4	Contusion/laceration	2.04 (1.05–3.97)	0.035	0.015

CI, confidence interval; EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hemorrhage.

Variables in the equation ($p < 0.2$): mechanism of injury blunt vs. penetrating; GCS score ≤8 vs. >8; hypotension Yes vs. No; ISS ≥16 vs. <16; ISS ≥25 vs. <25; AIS head 3/5 Yes vs. No; vault fracture Yes vs. No; contusion or laceration Yes vs. No; EDH/SDH/SAH Yes vs. No. The variable "age group" was forced into the regression.

criteria of coagulopathy are clinically relevant and significantly impact outcomes following severe head injury.

In the investigation by Miner et al.,[16] the frequency of abnormal coagulation tests was directly related to the extent of the brain injury; increasing from 52% in mild TBI to 87% in severe TBI. Similarly, in this investigation, the incidence of coagulopathy increased in a stepwise fashion with escalating head AIS amounting to ~90% in victims of devastating head injury. This observation is in accordance with previous studies.[15–17] Moreover, in the current analysis, penetrating head injury proved to result in a significantly higher coagulopathy rate compared with their blunt head injured counterparts that is most likely a manifestation of the massive brain lesions in these instances.

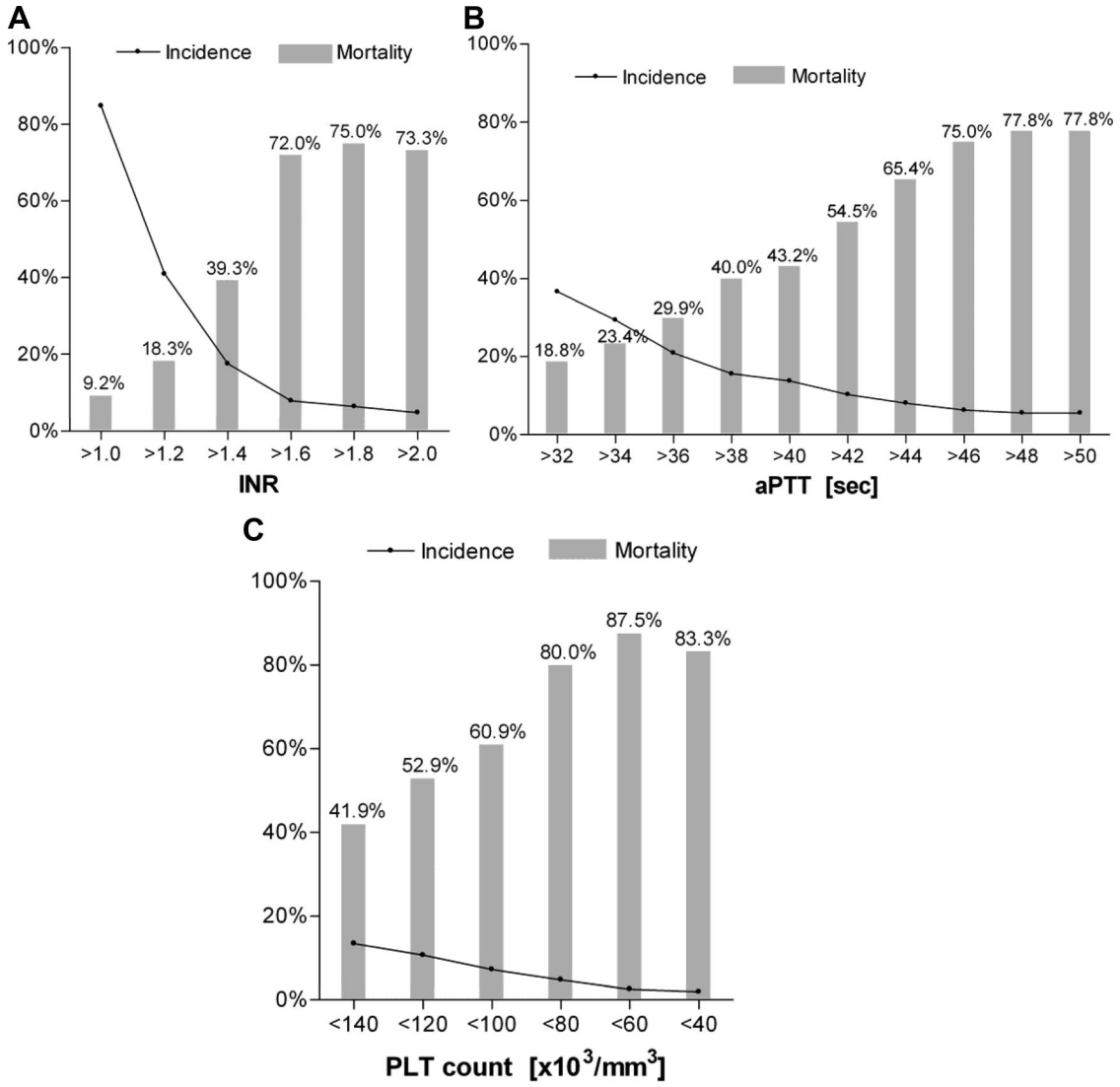
Moreover, age-related factors seem to impact the development of TBI coagulopathy among pediatric patients. With advancing age, the rate of coagulopathy increased significantly from 26% in patients aged 3 years or younger to almost 51% in adolescent patients. Differences in demographics, injury mechanisms, and TBI severity between the different age groups were controlled for in this analysis. Physiologic derangements occurring early after sTBI and contributing to coagulopathy, including hypothermia, hypoxia, hypoperfusion, and the release of proinflammatory cytokines, may be better compensated in early childhood.

TABLE 5. Hospital and SICU LOS and Mortality in Pediatric Isolated sTBI With and Without Coagulopathy

	All Patients (n = 320)	With Coagulopathy (n = 137)	Without Coagulopathy (n = 183)	*p*	Adjusted *p**	Adjusted OR/Mean Difference (95% CI)*
SICU LOS (d), mean ± SD	6.5 ± 6.9	8.5 ± 8.5	4.3 ± 3.6	<0.001	0.011	2.29 (0.53–4.05)
Hospital LOS (d), mean ± SD	8.6 ± 9.7	12.6 ± 12.3	5.7 ± 5.5	<0.001	<0.001	4.30 (2.13–6.47)
Mortality	7.8% (25/320)	17.5% (24/137)	0.5% (1/183)	<0.001	0.912	1.21 (0.04–35.35)

SD, standard deviation; OR, odds ratio; CI, confidence interval; MOI, mechanism of injury; EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hemorrhage; SICU, surgical intensive care unit; LOS, length of stay.

* Adjusted for age, penetrating MOI; GCS score ≤8; GCS score 13–15; hypotension; ISS; AIS head 3; AIS head 5; contusion/laceration; and EDH/SDH/SAH.



Abbreviations: INR, International Normalized Ratio; aPTT, Activated Partial Thromboplastin Time; PLT, Platelet; sTBI, Severe Traumatic Brain Injury

Figure 3. Incidence and case fatality rate at corresponding INR (*A*), aPTT (*B*), and platelet-count (*C*) values in pediatric isolated sTBI.

There is scant literature establishing independent risk factors for the development of coagulopathy after pediatric sTBI. Affonseca et al.[15] reviewed 301 pediatric patients with mild to severe traumatic brain injuries and found the severity of brain injury, the diagnosis of brain edema on initial computed tomogaphic scan, and the presence of concomitant chest or abdominal injury to be independently associated with the development of coagulopathy. For adult isolated sTBI patients, our previous investigations revealed a GCS score of $\leq$8, an ISS $\geq$16, the presence of cerebral edema, subarachnoid hemorrhage, midline shift, hypotension, and hypoperfusion (base deficit $>$6 mmol/L) on hospital admission to be independently associated with coagulopathy.[1,18] The present analysis observes similar independent associations in isolated sTBI pediatric patients. Markers of severe head injury, including a low GCS and intraparenchymal contusions and lacerations, increasing age, and an ISS $\geq$16 proved to be independent risk factors for the development of coagulopathy.

Coagulopathy has been associated with poor in-hospital and long-term outcomes after head injury in children.[9,11–13,16,19] In the study by Vavilala et al.,[19] coagulopathy, defined by a fibrin degradation product level $>$1,000 μg/mL, significantly predicted poor outcomes characterized by Glasgow Outcome Scale score $\leq$3. Similarly, in the study by Chiaretti et al.,[11] children with extended aPTT, elevated fibrin degradation product, decreased fibrinogen, and low platelet count had a significantly worsened outcome including both mortality and long-term neurologic deficit (Glasgow Outcome Scale score, 3). With regard to in-hospital outcomes, the present analysis demonstrates that SICU and hospital LOS are adversely influenced by the development of coagulopathy in the studied cohort. We noted a significantly increased crude mortality in

patients suffering TBI coagulopathy. To validate the true impact of clotting disorders on mortality, we performed a rigorous logistic regression adjusting for differences in overall and head injury severities, and specific head injuries. After adjusting for confounders, the significant discrepancy in survival was lost in noncoagulopathic versus coagulopathic patients. This is in contrast to previously published results in pediatric[11,16] and adult[1,6] sTBI patients reporting a strong relationship between coagulopathy and mortality. As observed in previous studies, children may recover more quickly and more frequently from serious injuries than adult victims of severe head injury.[20,21]

Although this is one of the largest studies investigating coagulopathy in pediatric isolated sTBI patients, there are several limitations, the most important being the retrospective nature of data analysis. Second, the impact of therapeutic intervention on outcomes, the effect of procoagulant therapy, including transfusion of fresh-frozen plasma, platelets, cryoprecipitate, or factor VIIa on in-hospital outcomes could not be determined. Finally, data regarding long-term outcome were not available for analysis.

CONCLUSION

Incidence of coagulopathy in children suffering isolated sTBI is exceedingly high at 40% and reflects the head injury severity. A depressed GCS, increasing age, ISS $\geq$16, and intraparenchymal lesions proved to be independently associated with TBI coagulopathy.

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