Journal of Trauma and Acute Care Surgery, Publish Ahead of Print
DOI: 10.1097/TA.0000000000004013

# Crystalloid Volume is Associated with Short Term Morbidity in Children with Severe Traumatic Brain Injury: An Eastern Association for the Surgery of Trauma Multicenter Trial Post-Hoc Analysis

Taleen A. MacArthur[1], Adam M. Vogel[2], Amy E. Glasgow[1], Suzanne Moody[3], Meera Kotagal[3], Regan F. Williams[4], Mark L. Kayton[5], Emily C. Alberto[6], Randall S. Burd[6], Thomas J. Schroeppel[7], Joanne E. Baerg[8], Amanda Munoz[8], William B. Rothstein[9], Laura A. Boomer[9], Eric M. Campion[10], Caitlin Robinson[10], Rachel M. Nygaard[11], Chad J. Richardson[11], Denise I. Garcia[12], Christian J. Streck[12], Michaela Gaffley[13], John K. Petty[13], Mark Ryan[14], Samir Pandya[14], Robert T. Russell[15], Brian K. Yorkgitis[16], Jennifer Mull[16], Jeffrey Pence[17], Matthew T. Santore[18], Denise B. Klinkner[1], Shawn D. Safford[19], Tanya Trevilian[19], Aaron R. Jensen[20], David P. Mooney[21], Bavana Ketha[22], Melvin S. Dassinger III [22], Anna Goldenberg-Sandau[23], Richard A. Falcone Jr[3], Stephanie F. Polites[1]

[1] Mayo Clinic, Rochester, Minnesota

[2] Texas Children's Hospital, Houston, Texas

[3] Division of Pediatric General and Thoracic Surgery Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[4] Le Bonheur Children's Hospital, Memphis, Tennessee

[5] Jersey Shore University Medical Center, Hackensack-Meridian Health Network, Neptune, New Jersey

[6] Children's National Hospital, Washington, DC

[7] UCHealth Memorial Hospital, Colorado Springs, Colorado

[8] Loma Linda University, Loma Linda, California

[9] Children's Hospital of Richmond, Virginia Commonwealth University, Richmond, Virginia

[10] Denver Health Medical Center, Denver, Colorado

[11] Hennepin Healthcare, Minneapolis, Minnesota

[12] The Medical University of South Carolina, Charleston, South Carolina

[13] Wake Forest Baptist Medical Center, Brenner Children's Hospital, Winston-Salem, North Carolina

[14] Children's Health Dallas, Dallas, Texas

[15] Children's of Alabama, Birmingham, Alabama

[16] College of Medicine, University of Florida Jacksonville, Jacksonville, Florida

[17] Dayton Children's Hospital, Dayton, OH

[18] Children's Healthcare of Atlanta, Atlanta, Georgia

[19] Carilion Children's Hospital, Carilion Roanoke Memorial Hospital, Roanoke, Virginia

[20] Benioff Children's Hospital, University of California San Francisco, San Francisco, California

[21] Boston Children's Hospital, Boston, Massachusetts

[22] Arkansas Children's Hospital, Little Rock, Arkansas

[23] Cooper University Hospital, Camden, New Jersey

**Author Contact Information**:

Taleen A. MacArthur, MD: macarthur.taleen@mayo.edu, ORCID: 0000-0001-6627-781X

Stephanie F. Polites, MD, MPH: Polites.Stephanie@mayo.edu, ORCID: 0000-0003-1947-5439

Adam M. Vogel, MD: amvogel@texaschildrens.org

Suzanne Moody, MPA: suzanne.moody@cchmc.org

Meera Kotagal, MD: meera.kotagal@cchmc.org, ORCID: 0000-0002-3327-381X

Regan F Williams, MD, MSE: rfwillia@uthsc.edu

Mark L. Kayton, MD: mark.kayton@hmhn.org

Randall S. Burd, MD, PhD: rburd@childrensnational.org, ORCID: 0000-0003-4465-9117

Emily C. Alberto, MD: ealberto@childrensnational.org

Thomas J. Schroeppel, MD, MS: Thomas.Schroeppel@uchealth.org

Joanne E. Baerg, MD: joanne_elaine@verizon.net

Amanda Munoz, MD: amamunoz@llu.edu

William B. Rothstein, MD: william.rothstein@vcuhealth.org

Eric M. Campion, MD: eric.campion@dhha.org

Caitlin Robinson, MPH, CRA: caitlin.robinson@dhha.org

Rachel M. Nygaard, PhD: rachel.nygaard@hcmed.org, 0000-0002-2807-519X

Chad J. Richardson, MD: chad.richardson@hcmed.org

Denise I. Garcia, MD, M.Ed: garciad@musc.edu

Christian J. Streck, MD: streck@musc.edu

Michaela Gaffley, MD: mgaffley@wakehealth.edu

John K. Petty, MD: jpetty@wakehealth.edu

Samir Pandya, MD: Samir.pandya@UTSouthwestern.edu

Mark Ryan, MD: mark.ryan@utsouthwestern.edu

Robert T. Russell, MD, MPH: robert.russell@childrensal.org, ORCID: 0000-0002-8531-4249

Brian K. Yorkgitis, DO: brian.yorkgitis2@jax.ufl.edu

Jennifer Mull, RN: jennifer.mull@jax.ufl.edu

Jeffrey Pence, MD: pencej@childrensdayton.org

Matthew T. Santore, MD: matthew.santore@emory.edu

Denise B. Klinkner, MD, M.Ed: Klinkner.denise@Mayo.edu

Shawn D. Safford, MD, MAS: sdsafford@carilionclinic.org

Tanya Trevilian, MSN, RN, CCRN-K, CPN: TLTREVILIAN@carilionclinic.org

Aaron R. Jensen, MD, M.Ed: aaron.jensen@ucsf.edu

David P. Mooney, MD, MPH: David.Mooney@childrens.harvard.edu

Bavana Ketha, MD: bavana.ketha@gmail.com

Melvin S. Dassinger III, MD: dassingermelvins@uams.edu

Anna Goldenberg-Sandau, DO: goldenberg-anna@cooperhealth.edu

**Corresponding Author & Requests for Reprints:**

Taleen A. MacArthur

Department of Surgery, Mayo Clinic, Rochester, MN

200 First Street SW, Rochester, MN 55905

Phone: (507) 774-2623, Email: macarthur.taleen@mayo.edu

**Funding Support:** This work was supported in part by the Childress Institute for Pediatric Trauma

**Conflict of Interest Statement:** There are no conflicts of interest to report for any author.

**Meeting Presentation**: This study was presented at the 36th Annual Scientific Assembly for the Eastern Society for the Surgery of Trauma (EAST), January 17-21,2023 in Lake Buena Vista, Florida.

**Author Contribution Statement:**

SFP, DBK, AMV, RAF, AEG contributed to study design, data acquisition, data analysis, data interpretation, critical manuscript revisions and final manuscript approval. TAM contributed to study design, data acquisition, data analysis, manuscript writing and final manuscript approval. SM, MK, and RW contributed to study design, data acquisition and analysis, critical manuscript revisions and final approval. MLK, ECA, RSB, TJS, JEB, AM, WBR, LAB, EMC, CR, RMN, CJR, DIG, CJS, MG, JKP, MR, SP, RTR, BKY, JM, JP, MTS, SDS, TT, ARJ, DPM, BK, MSD, AGS contributed to data acquisition, data interpretation, critical manuscript revision and final approval.

**Social Media Information:**

- *Media Summary:* Pediatric trauma patients with severe TBI received more crystalloid than those without. Excessive crystalloid may be associated with worsened outcomes in pediatric severe TBI patients who received ≥ 1 crystalloid bolus.
- *Hashtags:* #trauma, #pediatricsurgery, #TBI, #resuscitation, #coagulopathy
- *Author Handles*: @taleenmacarthur @rachelnygaard, @mkotagal, @russelrt132

**ABSTRACT:**

**Objective:** This study examined differences in clinical and resuscitation characteristics between injured children with and without severe traumatic brain injury (sTBI) and aimed to identify resuscitation characteristics associated with improved outcomes following sTBI.

**Methods:** This is a *post-hoc* analysis of a prospective, observational study of injured children <18 years old (2018-2019) transported from the scene, with elevated shock index pediatric-adjusted on arrival and head Abbreviated Injury Scale (AIS) score ≥3. Timing and volume of resuscitation products were assessed using Chi-squared t-test, Fisher's exact t-test, Kruskal-Wallis, and multivariable logistic regression analyses.

**Results:** There were 142 patients with sTBI and 547 with non-sTBI injuries. sTBI patients had lower initial hemoglobin (11.3 vs. 12.4, p < .001), greater initial INR (1.4 vs. 1.1, p < .001), greater ISS (25 vs. 5, p <.001), greater rates of ventilator (59% vs. 11%, p <.001) and ICU requirement (79% vs. 27%, p< .001), and more inpatient complications (18% vs. 3.3%, p< .001). sTBI patients received more pre-hospital crystalloid (25% vs. 15 %, p=.008), ≥1 crystalloid boluses (52% vs.24%, p<.001), and blood transfusion (44 % vs.12%, p<.001) than non-sTBI patients. Among sTBI patients, receipt of ≥1 crystalloid bolus (n=75) was associated with greater ICU need (92% vs.64%, p<.001), longer median ICU (6 vs.4 days, p = 0.027) and hospital stay (9 vs.4 days, p<.001), and more in-hospital complications (31% vs. 7.5%, p =0.003) than those who received <1 bolus (n=67). These findings persisted after adjustment for injury severity score (OR 3.4-4.4, all p < .010).

**Conclusion:** Pediatric trauma patients with sTBI received more crystalloid than those without sTBI despite having a greater INR at presentation and more frequently requiring blood products. Excessive crystalloid may be associated with worsened outcomes, including in-hospital mortality, seen among pediatric sTBI patients who received ≥ 1 crystalloid bolus. Further attention to a crystalloid sparing, early transfusion approach to resuscitation of children with sTBI is needed.

**Level of Evidence:** IV

**Study Type:** Retrospective *post-hoc* analysis of a prospective observational cohort study

**Key Words:** trauma, pediatric, surgery, TBI, resuscitation

**INTRODUCTION**:

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in injured children. It is also associated with substantial monetary costs to the healthcare system.[1] Optimal resuscitation practices for TBI patients have long been debated. There is a balance needed between avoiding hypotension and hypoxia, which are associated with poor outcomes following TBI due to their impact on cerebral perfusion and minimizing cerebral edema.[2,3] Guidelines for TBI management focus on preventing secondary TBI due to cerebral hypoperfusion, which often involves fluid resuscitation in hypotensive patients.[3] No consensus guidelines on optimal fluid resuscitation practices in pediatric TBI patients currently exist.

Saline-based fluid resuscitation may be associated with improved outcomes in TBI compared to balanced crystalloids or albumin, as it generates less cerebral edema.[4,5] High-volume crystalloid resuscitation, however, has been associated with increased odds of mortality in this population.[6,7] Volume overload as result of fluid resuscitation may occur while attempting to maintain cerebral perfusion pressure.[8] One hypothesis for the association between high volume crystalloid resuscitation and mortality in TBI patients is that excessive crystalloid worsens the coagulopathy related to TBI.[9,10] Although underlying mechanisms are still being elucidated, the brain microenvironment appears to be procoagulant, with disruptions of the blood-brain barrier resulting in procoagulant factors being released systemically.[10] In pediatric trauma patients, severe TBI (sTBI) has been associated with prolonged fibrinolytic shutdown as measured by thromboelastography (TEG), with fibrinolytic shutdown being associated with poor outcomes.[11] Additionally, when there is coexisting hemorrhagic shock, sTBI has been associated with multiple TEG derangements, including impaired clot initiation, strength, and stability.[12]

Excessive resuscitation with plasma has been associated with fibrinolysis shutdown and poor prognosis in sTBI patients.[13] Whole blood-based resuscitation may improve hemodynamics with less crystalloid administration, a finding shown in clinical and animal studies.[14,15]

There is growing interest in determining optimal resuscitation of children with sTBI that accounts for the need to maintain cerebral perfusion pressures and mitigate coagulopathy. Our initial study, which included 712 pediatric trauma patients (< 18 years) with an elevated age-adjusted shock index (SIPA score) showed that receiving more than one crystalloid bolus and delayed transfusion were associated with worse outcomes among injured children overall.[16,17] The objective of this study was to determine differences in clinical characteristics, outcomes, and resuscitation characteristics between severely injured children with and without sTBI and to identify resuscitation characteristics associated with improved outcomes following sTBI. We hypothesize that children with severe sTBI will receive more crystalloid early in resuscitation than children without sTBI, and that administration of more than one crystalloid bolus will be associated with worsened clinical outcomes in sTBI patients.

**METHODS:**

*Study Design:*

This is a *post-hoc* analysis of a multi-institution prospective observational study that was conducted between April 2018 and September 2019.[16] Twenty-four centers participated, including 17 Level I pediatric trauma centers, three Level II pediatric trauma centers, and four Level I adult trauma centers. Local institutional review board (IRB) approval was obtained at each center. STROBE guidelines were used in study design, manuscript composition, and

formatting (Supplemental Digital Content 1, http://links.lww.com/TA/C986). Pediatric trauma patients <18 years old at the time of injury who presented with an elevated SIPA score on either their first or second set of vitals and were transported directly from the scene were included. SIPA score has been previously validated to identify severely injured children.[17] Exclusion criteria included: children with a normal SIPA score, >20% total body surface area burns, an isolated burn or inhalation injury, asphyxiation injuries, transfer from another facility, or transfer to the receiving trauma center via police or private vehicle. We also excluded from this analysis patients who arrived with non-survivable head injuries (head AIS = 6), or those who were deceased at the time of arrival (discharged as deceased from the resuscitation bay).

*Patient Enrollment and Data Collection:*

Patient demographic information, clinical characteristics, and outcomes were reviewed and recorded by each center. Variables collected included the volume and type of crystalloid and blood products received for each patient up to 30-hours from injury, including during the pre-hospital, emergency department (ED), and initial admission resuscitation. Only data for the index hospitalization was available for this patient cohort. Therefore, the endpoint for clinical data collection, including complication data was date of hospital discharge or in-hospital death. All data, including injury severity score (ISS) and organ system specific abbreviated injury score (AIS), were abstracted from each participating center's National Trauma Data Standard trauma registry (NTDS).[18] A crystalloid bolus was defined as 20 +/- 10 mL/kg of either 0.9% normal saline or lactated ringers solution. In this *post-hoc* analysis, we focused on patients with severe TBI (sTBI) at the time of injury, which we defined as head AIS severity scale of 3 or greater. Patients with head AIS of 6 were excluded, as these injuries are considered non-survivable.

Patients without sTBI included all other enrolled pediatric trauma patients, including those with head AIS severity scale 0-2. Patients without sTBI who were otherwise severely injured, defined as an injury in any other organ system with an AIS score ≥ 3, were also examined in subgroup analysis.

*Statistical Analysis:*

Statistical analysis was performed using SAS Version 9.4 (Cary, NC, USA). Results are presented as medians and interquartile ranges (IQR) for continuous variables and n (%) for categorical variables unless otherwise specified. Kruskal-Wallis test for significance was performed for continuous variables. Chi-square or Fisher's exact t-test used as appropriate for categorical variables. Univariate and multivariable logistic regression analysis, controlling for ISS as confounding variable, was used to assess the relationship between resuscitation characteristics and clinical outcomes in sTBI and non-sTBI patients. Specific primary clinical outcomes examined included: intensive care unit (ICU) admission, extended hospital length of stay (> 15 days) and development of any complications while in hospital. Variables chosen for multivariable analysis adjustment were both clinically and statistically significant on univariate regression. Due to limited events, variables deemed the most clinically significant by the study team were selected. Secondary clinical outcomes examined included: need for blood product transfusion, need for mechanical ventilation, and ICU length of stay. Associations between crystalloid volume and outcomes are reported as odds ratios (OR) with 95% confidence intervals (95% CI). $P < 0.05$ was considered statistically significant. Deviance and Pearson goodness of fit statistics were used to assess goodness of fit. Resuscitation products included all crystalloid and blood products administered in the first 30-hours following injury, including in the pre-hospital phase.

**RESULTS:**

*Demographic and Clinical Characteristics:*

From the parent study for this data set, there were a total of 712 patients that met inclusion and were enrolled in the initial study.[16] Of these 712 patients, twenty three patients were excluded due to non-survivable injuries at the time or arrival, leaving 689 patients for analysis. There were 142 pediatric trauma patients with sTBI and 547 without sTBI enrolled in this study. There were no differences in age, sex, or injury mechanism between the two groups (**Table 1**). Similar rates of smoking were observed in both groups (5.0% vs. 6.1%, $p > 0.99$). Patients with sTBI were more severely injured, with lower median Glasgow Coma Scale (GCS) score at presentation and greater ISS than non-sTBI patients. sTBI patients also had lower median hemoglobin, greater INR, greater rates of ICU admission, ventilator requirement, complications, in-hospital mortality, and longer hospital length of stay than patients without sTBI (**Table 1**).

Among the sTBI patients, 60 (42.2%) had head AIS of 3, 43 (30.2%) had head AIS of 4, 39 (27.4%) had head AIS of 5. Among the non-sTBI patients, 71 (12.9%) had head AIS of 1, and 71 (12.9%) had head AIS of 2. Both groups had similar median time (minutes) between injury and arrival to the receiving trauma center (sTBI 43.0 vs. non-sTBI 44.0, $p = 0.508$). Fewer patients in the sTBI group were discharged home (84 (59.1%) vs. 469 (85.7%), $p < 0.001$), with more patients in the sTBI group being discharged to a rehabilitation facility or skilled nursing facility (32 (22.5%) vs. 15 (2.7%) , $p < 0.001$), or long-term acute care hospital (8 (6.6%) vs. 5 (1.0%), $p < 0.001$). sTBI patients also had greater in-hospital mortality than non-sTBI patients (**Table 1**).

*Resuscitation Characteristics: sTBI vs. non-sTBI*

There was no difference in the percentage of patients receiving prehospital blood products in the sTBI and non-sTBI groups (3 (2.1%) vs. 3 (0.5%), p = 0.116), though the percentage of patients receiving pre-hospital blood products was low in both groups overall. More sTBI patients received blood products within the first 30-hours after injury than non-sTBI patients, as described in **Table 1.** More patients in the sTBI group received pre-hospital crystalloid than in the non-sTBI group (36 (25.4%) vs. 81 (14.8%), p = 0.008). In the sTBI group, 51 (35.9%) patients received one crystalloid bolus, 16 (11.3%) received two boluses, six (4.2%) received three boluses, and two (1.4%) received >3 crystalloid boluses. In the non-sTBI group, 101 (18.5%) patients received one crystalloid bolus, 28 (5.1%) received two boluses, one (0.2%) received 3 boluses, and one (0.2%) received >3 crystalloid boluses. Twenty-six sTBI patients (18.3%) received hypertonic saline compared to six (1.1%) non-sTBI patients (p <0.0001). sTBI patients also received a greater mean volume of 3% hypertonic saline (HTS) than non-sTBI patients (56.0 mL vs. 2.1 mL, p < 0.001). These data include all fluids administered in the first 30-hours after injury, including pre-hospital resuscitation.

*sTBI Patients: ≥1 Crystalloid Bolus vs. <1 Crystalloid Bolus*

More patients with sTBI received ≥ 1 crystalloid bolus than non-sTBI patients (75 (52.8%) vs. 131 (23.9%), p < 0.001). sTBI patients that received one or more crystalloid boluses had greater rates of ICU admission and mechanical ventilation, longer median ICU length of stay, and more overall complications (**Table 2**). There was no difference in rate of 3% HTS administration between sTBI patients who received ≥ 1 crystalloid bolus and sTBI patients who received < 1 crystalloid bolus (17 (22.7%) vs. 9 (13.4%), p = 0.194).

On multivariable analysis of sTBI patients (n = 142), after adjusting for ISS, receipt of ≥ 1 crystalloid bolus remained independently associated with ICU admission, hospital stay > 15 days, and development of any in-hospital complication among sTBI patients (**Table 3**). To further control for the influence of ISS on outcomes, we performed multivariable logistic regression modeling on the subset sTBI patients with ISS > 16 only (n = 103) and found that receipt of ≥ 1 crystalloid bolus remained associated with extended hospital stay > 15 days when adjusting for ISS (OR 4.30, 95% CI: 1.5-12.4, p = 0.007). When multivariable modeling was performed with only the sTBI patients with ISS > 25 (n = 69), receipt of ≥ 1 crystalloid bolus was no longer significantly associated with extended hospital stay > 15 days when adjusting for ISS (OR 2.82 (95% CI 0.98-8.09), p = 0.054).

To better define the effects of larger crystalloid volumes on sTBI patients, we compared patients who received ≥ 2 crystalloid boluses (n = 24) to those who received < 2 crystalloid boluses (n = 118). Patients who received ≥ 2 crystalloid boluses were more likely to have a severe injury (AIS ≥ 3) in another organ system (17 (70.8%) vs. 57 (48.3%), p = 0.044), and were more likely to have received pre-hospital blood products, (1 (4.2%) vs. 2 (1.7%), p = 0.025).

*sTBI Patients vs. Other Severely Injured Patients*:

Patients with sTBI (n = 142) were compared to patients without sTBI who had severe injury in at least one other organ system rated with an AIS ≥ 3 (n = 130). Demographic and clinical characteristics of these two groups are outlined in **Table 4.** sTBI patients were younger, had greater rates of blunt injury, and were overall more severely injured with greater ISS than

severely injured non-sTBI patients (**Table 4**). Despite having lower median initial hemoglobin, sTBI patients were less likely to receive blood products first compared to severely injured non-sTBI patients (**Table 4**). sTBI patients again had greater rates of ICU admission and ICU length of stay, greater rates of mechanical ventilation, and greater in-hospital mortality compared to

*sTBI Patients Requiring Transfusion:*

Among the sTBI patients, 63 received blood product transfusion within 30-hours of injury while 79 did not. Transfused patients were older than patients that did not require transfusion (median age 3.0 years vs. 8.0 years, $p = 0.007$), and had a greater median ISS (28.0 vs. 19.0, $p < 0.001$) compared to sTBI patients that were not transfused. More transfused sTBI patients received pre-hospital crystalloid (23 (39.7%) vs. 13 (17.3%) , $p = 0.019$ ) but there was no difference in the number of patients receiving $\geq 1$ crystalloid bolus (37 (46.8%) vs. 38 (60.3%), $p = 0.110$) compared to non-transfused-sTBI patients. There was no difference in rates of 3% HTS administration between transfused and non-transfused sTBI patients (15 (23.8%) vs. 11 (13.9%), $p = 0.189$). Transfused patients had greater median presenting INR than patients that were not transfused (1.4 vs. 1.1, $p < 0.001$) as well as lower median presenting platelet levels (303,000 vs. 344,000, $p = 0.012$).

Overall median [IQR] blood product volumes (mL/kg) received were similar in the sTBI (n = 63) and non-sTBI (n = 68) groups (23.8 [11.9, 56.5] vs. 22.4 [11.8, 45.4], $p = 0.421$). Overall median volumes (mL/kg) of specific blood product type received were also similar between the sTBI and non-sTBI groups including red blood cells (sTBI n = 59, 16.3 [9.8, 33.3] vs. non-sTBI n = 63, 16.0 [10.5, 26.3], $p = 0.805$), plasma ( sTBI n = 38, 20.3 [10.0, 30.3] vs.

non-sTBI n= 40, 15.1 [7.1, 23.9], p = 0.130), and platelets (sTBI n = 20, 7.8 [4.1, 12.9] vs. non-sTBI n = 21, 5.8 [3.4, 8.7], p = 0.129). There was no difference in the rate of patients receiving a low ratio (< 1:2) of packed red blood cells to platelets between transfused sTBI patients and non-sTBI patients. There was also no difference in ratio of packed red blood cells to fresh frozen plasma between sTBI and non-sTBI patients among those who had available transfusion data (p = 0.140).

sTBI patients and otherwise severely injured non-sTBI patients also had similar overall frequency of blood transfusion within the first 30-hours following injury, though the severely injured non-sTBI patients were more likely to receive blood first before crystalloid (**Table 4**). Total median [IQR] blood product volumes (mL/kg) transfused were similar between the sTBI (n = 63) and severely injured non-sTBI (n = 50) groups (23.8 [11.9, 56.5] vs 25.7 [13.0, 50.0], p = 0.901). Total volumes (mL/kg) of specific blood products transfused were also similar between these two groups, including red blood cells (sTBI n = 59, 16.3 [9.8, 33.3] vs. severely injured non-sTBI n = 48, 17.5 [11.7, 28.8], p =0.956), plasma (sTBI n = 38, 20.3 [10.0, 30.3] vs. severely injured non-sTBI n = 33, 15.0 [6.3, 25.0], p = 0.123), and platelets (sTBI n = 20, 7.8 [4.1, 12.9], vs. non-sTBI n = 20, 5.6 [3.4, 8.8], n = 0.201).

**DISCUSSION:**

Optimal resuscitation practices for pediatric trauma patients with sTBI have not been well established. Previous studies, however, have shown that high volume crystalloid resuscitation is associated with poor outcomes in injured children, including prolonged duration of mechanical ventilation.[19] This study was a *post-hoc* analysis of data from a previously published multi-

institution study of resuscitation practices in pediatric trauma patients (all injury types), which found that administration of ≥ 1 crystalloid bolus was associated with worsened outcomes.[16] We found that in the subset of sTBI patients, receipt of ≥ 1 crystalloid bolus was associated with worse outcomes, including ICU admission, extended hospital length of stay, and development of in-hospital complications after adjusting for ISS.

While more severely injured patients are more likely to receive larger fluid volumes for resuscitation, the association between ≥ 1 crystalloid bolus and worsened outcomes in the sTBI patients persisted in this study even when adjusting for injury severity. In severely injured sTBI patients with ISS > 16, receipt of ≥ 1 crystalloid bolus was also associated with extended hospital stay > 15 days after adjusting for injury severity, though this did not hold for patients with ISS >25. It may be that the ISS > 25 group was underpowered to detect a significant association (n = 69), or that in patients with that injury severity level crystalloid volume has less of an impact. This association shows the potentially deleterious effects of excessive crystalloid resuscitation in pediatric trauma, and the need to balance optimizing cerebral perfusion and limiting crystalloid volume. This is in keeping with previously published work demonstrating that even following hemostatic blood-based resuscitation, high-volume crystalloid administration is associated with worse clinical outcomes, and negates the benefits of hemostatic resuscitation.[20] Patients in the sTBI group had a greater median presenting INR of 1.4 compared to 1.1 in the non-sTBI group, showing potential evidence of coagulation dysregulation. In pediatric trauma patients, including victims of abusive head trauma, an INR of ≥ 1.3 is associated with increased mortality and worsened outcomes, a potential marker of systemic dysregulation.[21, 22] These data suggest that TBI leads to coagulopathy, which can be worsened by excessive crystalloid resuscitation. These

data also suggest that small variations in coagulation parameters can be associated with worsened outcomes after trauma, particularly head injury.

In this study, sTBI patients were more likely than non-sTBI patients to require blood product transfusion. When compared to severely injured non-sTBI patients, sTBI patients were less likely to receive blood products first, despite similar rates of transfusion requirement within the first 30-hours of injury. This indicates that although severely injured children overall may have a similar resuscitation pattern with regard to frequency of blood and crystalloid administration, sTBI patients receive a blood forward approach less frequently than otherwise severely injured non-sTBI patients, despite ultimately having a similar overall transfusion frequency. The sTBI patients requiring blood product transfusion had significant markers or coagulation dysregulation, with a higher INR than those who were not transfused. These data suggest that although many sTBI patients eventually require blood products, they often do not receive them as early as severely injured non-sTBI patients. As more data is generated on the role of early blood-based resuscitation in pediatric trauma, just as it is now recommended in children with hemorrhagic shock, early blood-based resuscitation, particularly with whole blood, may have the dual benefit of limiting crystalloid volume and mitigating development of trauma-induced coagulopathy in pediatric sTBI patients.[23,24]

This study shows association between receipt of one or more crystalloid boluses and worsened outcomes in pediatric sTBI patients. Because this study was retrospective and observational, we are unable to establish a causal mechanism for the association seen between crystalloid administration and worsened outcomes in pediatric sTBI patients. High volume

crystalloid resuscitation after traumatic injury has been thought to worsen outcomes through volume overload and hemodilution. In children, a threshold of 60 cc/kg/ 24-hour period has been used to define high-volume crystalloid resuscitation and has been associated with prolonged ICU length of stay without any survival benefit.[25] In comparison, in this study bolus volumes of 20 mL/kg +/- 10 mL were associated with worsened outcomes in pediatric sTBI patients, even when accounting for injury severity. These data highlight the fact that even relatively low volumes of crystalloid can impact physiology and coagulation in pediatric trauma patients with sTBI and thus should be used judiciously. These findings also provide evidence supporting early blood product-based resuscitation to limit crystalloid volume, even in sTBI patients who may not be in hemorrhagic shock.

This study has several limitations. Due to its retrospective nature, we are unable to show any causal mechanism between crystalloid administration in sTBI patients and outcomes, only association. The literature has consistently shown that both hypotension and hypoxia are associated with poor outcomes in pediatric TBI patients, and that timely correction of these physiologic parameters is associated with improved clinical outcomes. The present analysis did not include physiologic analysis to assess how hypotension and hypoxia may have impacted our outcomes or changed with varying volumes of crystalloid resuscitation, but this is a notable area for future study, and a gap between this study and the existing literature.[26] In data analysis we were able to control for ISS when assessing the association between crystalloid volume and outcomes on multivariable analysis. However, ISS is only one method of measuring injury severity. We were unable to control for other factors that may have contributed to patients receiving varying crystalloid volumes, such as transport time from the scene that may also have

impacted our findings. We had limited coagulation data available within this data set, such as TEG parameters, which could have provided more insight into the coagulation status of the sTBI patients. Additionally, certain laboratory markers including base deficit and lactate that could have provided insight into patient illness severity, clinical picture, and resuscitation status were not included in this analysis. This data set also included only patients that presented with an elevated SIPA score, biasing our findings towards more severely ill patients. Additionally, this data set is biased towards a younger patient cohort as some participating pediatric trauma centers had age-limited admission criteria, as such we may be missing some adolescent patients who would have been triaged as adults and make up much of the TBI patient population. Given the limitations of this data set, we are unable to make specific clinical recommendations. However, this study does show the need for prospective interventional studies to establish and confirm best resuscitation practices for pediatric sTBI patients.

**Conclusion:**

Pediatric trauma patients with sTBI received more crystalloid than those without sTBI despite having a greater INR at presentation and more frequently requiring blood products. Excessive crystalloid may be associated with worsened outcomes, including in-hospital mortality, seen among pediatric sTBI patients who received ≥ 1 crystalloid bolus. Further attention to a crystalloid sparing, early transfusion approach to resuscitation of children with sTBI is needed.

**REFERENCES:**


1. Shi J, Xiang H, Wheeler K, Smith GA, Stallones L, Groner J, et al. Costs, mortality likelihood and outcomes of hospitalized US children with traumatic brain injuries. *Brain Inj*. 2009; 23(7):602-11.

2. Caplan HW, Cox CS. Resuscitation Strategies for Traumatic Brain Injury. *Curr Surg Rep*. 2019; 7(7):14.

3. Orliaguet GA, Meyer PG, Baugnon T. Management of critically ill children with traumatic brain injury. *Paediatr Anaesth.* 2008; 18(6):455-61.

4. Lombardo S, Smith MC, Semler MW, Wang L, Dear ML, Lindsell CJ, et al. Isotonic Solutions and Major Adverse Renal Events Trial (SMART) Investigators and Vanderbilt Learning Healthcare System Platform Investigators. Balanced Crystalloid versus Saline in Adults with Traumatic Brain Injury: Secondary Analysis of a Clinical Trial. *J Neurotrauma*. 2022; 39(17-18):1159-1167.

5. Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. *Crit Care.* 2020; 24(1):693.

6. Mbadiwe N, Georgette N, Slidell MB, McQueen A. Higher Crystalloid Volume During Initial Pediatric Trauma Resuscitation is Associated With Mortality. *J Surg Res*. 2021; 262:93-100.

7. Coons BE, Tam S, Rubsam J, Stylianos S, Duron V. High volume crystalloid resuscitation adversely affects pediatric trauma patients. *J Pediatr Surg*. 2018; 53(11):2202-2208.

8. Stulce C, Reisner A, Kane JM, Shin HS, McCracken C, Williamson J, et al. Fluid Overload in Pediatric Severe Traumatic Brain Injury. *Pediatr Crit Care Med*. 2020; 21(2):164-169.

9. Ko A, Harada MY, Barmparas G, Smith EJT, Birch K, Barnard ZR, et al. Crystalloid

Resuscitation after Traumatic Brain Injury. *Am Surg.* 2017; 83(12):1447-1452.

10. Zhang J, Jiang R, Liu L, Watkins T, Zhang F, Dong JF. Traumatic brain injury-associated coagulopathy. *J Neurotrauma*. 2012; 29(17):2597-605.

11. Leeper CM, Neal MD, McKenna CJ, Gaines BA. Trending Fibrinolytic Dysregulation: Fibrinolysis Shutdown in the Days After Injury Is Associated With Poor Outcome in Severely Injured Children. *Ann Surg*. 2017; 266(3):508-515.

12. Cucher D, Harmon L, Myer B, et al. Critical traumatic brain injury is associated with worse coagulopathy. *J Trauma Acute Care Surg*. 2021; 91(2):331-335.

13. Leeper CM, Neal MD, Billiar TR, Sperry JL, Gaines BA. Overresuscitation with plasma is associated with sustained fibrinolysis shutdown and death in pediatric traumatic brain injury. *J Trauma Acute Care Surg*. 2018; 85(1):12-17.

14. Zusman BE, Dixon CE, Jha RM, Vagni VA, Henchir JJ, Carlson SW, et al. Choice of Whole Blood versus Lactated Ringer's Resuscitation Modifies the Relationship between Blood Pressure Target and Functional Outcome after Traumatic Brain Injury plus Hemorrhagic Shock in Mice. *J Neurotrauma*. 2021; 38(20):2907-2917.

15. Zusman BE, Kochanek PM, Bailey ZS, Leung LY, Vagni VA, Okonkwo DO, et al. Multifaceted Benefit of Whole Blood Versus Lactated Ringer's Resuscitation After Traumatic Brain Injury and Hemorrhagic Shock in Mice. *Neurocrit Care*. 2021; 34(3):781-794.

16. Polites SF, Moody S, Williams RF, Kayton ML, Alberto EC, Burd RS, et al. Timing and volume of crystalloid and blood products in pediatric trauma: An Eastern Association for the Surgery of Trauma multicenter prospective observational study. *J Trauma Acute Care Surg.* 2020; 89(1):36-42.

17. Acker SN, Ross JT, Partrick DA, Tong S, Bensard DD. Pediatric specific shock index

accurately identifies severely injured children. *J Pediatr Surg*. 2015; 50(2):331–334.

18. American College of Surgeons. National Trauma Data Standard (NTDS). Available at: https://www.facs.org/quality-programs/trauma/tqp/center-programs/ntdb/ntds. Accessed November 9, 2022

19. Moulton AW, Schauer SG, Borgman MA. Prolonged Mechanical Ventilation in Pediatric Trauma Patients in a Combat Zone. *Pediatr Crit Care Med.* 2022; 23(12):1009-1016.

20. Schauer SG, April MD, Becker TE, Cap AP, Borgman MA. High crystalloid volumes negate benefit of hemostatic resuscitation in pediatric wartime trauma casualties. *J Trauma Acute Care Surg*. 2020; 89(2S Suppl 2):S185-S191.

21. Leeper CM, Nasr I, McKenna C, Berger RP, Gaines BA. Elevated admission international normalized ratio strongly predicts mortality in victims of abusive head trauma. *J Trauma Acute Care Surg.* 2016; 80(5):711-6.

22. Leeper CM, Kutcher M, Nasr I, McKenna C, Billiar T, Neal M, et al. Acute traumatic coagulopathy in a critically injured pediatric population: Definition, trend over time, and outcomes. *J Trauma Acute Care Surg.* 2016; 81(1):34-41.

23. Russell RT, Esparaz JR, Beckwith MA, Abraham PJ, Bembea MM, Borgman MA, et al Pediatric traumatic hemorrhagic shock consensus conference recommendations. *J Trauma Acute Care Surg.* 2023; 94(1S Suppl 1):S2-S10.

24. Leeper CM, Yazer MH, Triulzi DJ, Neal MD, Gaines BA. Whole Blood is Superior to Component Transfusion for Injured Children: A Propensity Matched Analysis. *Ann Surg.* 2020; 272(4):590-594.

25. Elkbuli A, Zajd S, Ehrhardt JD Jr, McKenney M, Boneva D. Aggressive Crystalloid Resuscitation Outcomes in Low-Severity Pediatric Trauma. *J Surg Res.* 2020; 247:350-355.

26. Kannan N, Wang J, Mink RB, Wainwright MS, Groner JI, Bell MJ, et al. Timely Hemodynamic Resuscitation and Outcomes in Severe Pediatric Traumatic Brain Injury: Preliminary Findings. *Pediatr Emerg Care.* 2021; 34(5):325-329.

**Supplemental Digital Content:**

SCD1:

This supplemental Digital Content (SCD1) contains the completed STROBE checklist utilized in the generation of this manuscript.

**Figure 1**: **Patient Enrollment Flow Diagram**

sTBI = severe TBI (Head AIS ≥ 3)

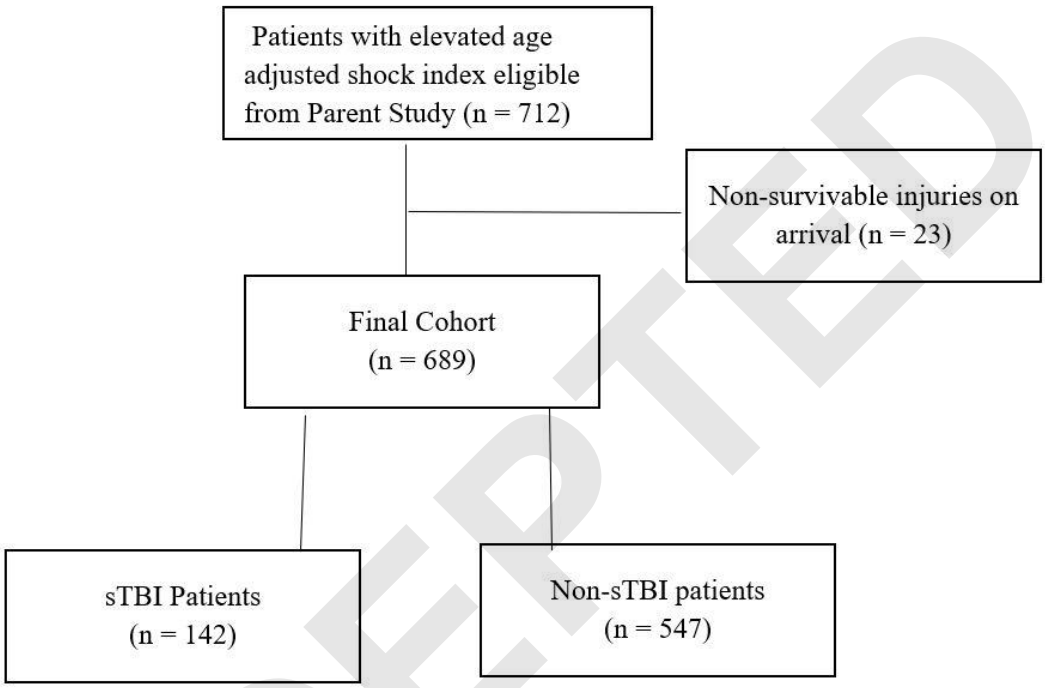


**Table 1**: **Demographic and Clinical Characteristics of Patients with Severe Traumatic Brain Injury (sTBI) vs. Those without sTBI**

| | **sTBI (Head AIS ≥ 3) n= 142** | **No sTBI (Head AIS< 3) n= 547** | **p-value** |
|---|---|---|---|
| **Age (years)** | 6.0 | 7.0 | .076 |
| **Sex (n% male) ^** | 78 (54.9%) | 270 (51.6%) | .485 |
| **Injury type (n% blunt)** | 131 (92.3%) | 458 (87.7%) | .132 |
| **Initial GCS** | 10.0 | 15.0 | **< .001** |
| **ISS** | 25.0 | 5.0 | **< .001** |
| **Initial hemoglobin** | 11.3 | 12.4 | **< .001** |
| **INR (mean, SD)** | 1.4 (0.4) | 1.1 (0.3) | **< .001** |
| **Blood product transfusion in first 30-hours from injury (n %)** | 63 (44.4%) | 68 (12.5%) | **< .001** |
| **ICU admission (n%)** | 112 (78.9%) | 146 (26.7%) | **< .001** |
| **Ventilator requirement (n%)** | 84 (59.2%) | 63 (11.5%) | **< .001** |
| **Ventilator days (mean, SD)** | 9.2 (16.9) | 3.3 (3.1) | **.001** |
| **Hospital Days (mean, SD)** | 13.0 (18.0) | 4.0 (7.4) | **<.001** |
| **Any complication (n%)**<br>**Pneumonia**<br>**Re-intubation**<br>**ALI/ARDS**<br>**DVT or PE**<br>**Blood Stream Infection**<br>**UTI**<br>**Sepsis**<br>**Other Complication** | 28 (19.7%)<br>5 (3.5%)<br>3 (2.1%)<br>1 (0.7%)<br>3 (2.1%)<br>1 (0.7%)<br>1 (0.7%)<br>1 (0.7%)<br>13 (9.2%) | 21 (3.8%)<br>0 (0.0%)<br>3 (0.5%)<br>1 (0.2%)<br>3 (0.5%)<br>1 (0.2%)<br>0 (0.0%)<br>1 (0.2%)<br>12 (2.2%) | **<.001**<br>**< .001**<br>**.**106<br>.206<br>.122<br>.370<br>.206<br>.370<br>**<.001** |
| **Received TXA** | 11 (7.7%) | 8 (1.5%) | **<.001** |
| **In-hospital mortality*** | 20 (14.1%) | 7 (2.8%) | **<.001** |

| | | | |
|---|---|---|---|
| **(n%)** | | | |

**Table 1**: Results presented as median or n (%) unless otherwise specified. ^Sex not available for 24 of the non-TBI patients; *mortality not available for 41 non-TBI patients. GCS = Glasgow coma score, ISS = injury severity score, INR = international normalized ratio, ICU = intensive care unit, ALI/ARDS = acute lung injury or acute respiratory distress syndrome, DVT or PE = deep vein thrombosis or pulmonary embolism, UTI = urinary tract infection, TXA = tranexamic acid

**Table 2: Comparison of sTBI Patients who received 1+ crystalloid bolus vs. < 1 crystalloid bolus within 30-hours of injury**

| | 1+ Bolus (n=75) | <1 bolus (n=67) | p-value |
|---|---|---|---|
| **Age (years)** | 9.0 | 5.0 | .875 |
| **Sex (n% male) ^** | 41 (54.7%) | 37 (55.2%) | .947 |
| **Injury type (n% blunt)** | 70 (93.3%) | 61 (91.0%) | .756 |
| **Initial GCS** | 5.0 | 6.0 | **.031** |
| **ISS** | 27.0 | 21.0 | **.010** |
| **Blood product transfusion Within first 30-hours of injury (n%)** | 38 (50.7%) | 25 (37.3%) | .110 |
| **Hospital Days (median, IQR)** | 10.0 (4.0, 24.0) | 4.0 (2.0, 9.0) | **<.001** |
| **ICU Admission (n%)** | 69 (92.0%) | 43 (64.2%) | **< .001** |
| **ICU Days (median, IQR)** | 6.0 (2.0, 15.07) | 4.0 (2.0, 9.0) | **.027** |
| **Mechanical ventilation (n%)** | 55 (73.3%) | 29 (43.3%) | **<.001** |
| **Overall Complications (n%)** | 23 (30.6%) | 5 (7.5%) | **.003** |
| **Pneumonia** | 4 (5.3%) | 1 (1.5%) | .215 |
| **Re-intubation** | 3 (4.0%) | 0 (0.0%) | .098 |
| **ALI/ARDS** | 0 (0.0%) | 1 (1.5%) | .288 |
| **DVT or PE** | 2 (2.7%) | 1 (1.5%) | .627 |
| **Blood Stream Infection** | 1 (1.3%) | 0 (0.0%) | .343 |
| **UTI** | 0 (0.0%) | 1 (1.5%) | .288 |
| **Sepsis** | 1 (1.3%) | 0 (0.0%) | .343 |
| **Other Complication*** | 12 (16.0%) | 1 (1.5%) | **.002** |

**Table 2:** Results presented as median for continuous variables or n (%) for categorical variables unless otherwise specified. ICU = intensive care unit, ALI/ARDS = acute lung injury/acute respiratory distress syndrome, DVT = deep vein thrombosis, PE = pulmonary embolism. *Other complications include: unplanned level of care escalation, airway tear, wound infection, pressure ulcer, development, stroke, significant electrolyte derangements, clostridium difficile infection, hypothalamic dysfunction, seizures.

**Table 3: Multivariable Analysis of Clinical Outcomes in Severe TBI (sTBI) Patients (n = 142) Based on Crystalloid Volume Administered and Injury Severity**

| All sTBI Patients (Head AIS ≥ 3) n = 142 | Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| **ICU Admission (Deviance: 0.5344, Pearson 0.1155)** | | | |
| ≥ 1 Crystalloid bolus | 4.4 | 1.45-13.65 | **.009** |
| ISS | 1.2 | 1.1-1.3 | **>.001** |
| **Extended Hospital Stay (> 15 Days) * (Deviance: 0.0565, Pearson 0.1668)** | | | |
| ≥ 1 Crystalloid bolus | 3.4 | 1.5-8.0 | **.005** |
| ISS | 1.1 | 1.0-1.1 | **.002** |
| **Any In-Hospital Complication (Deviance: 0.1674, Pearson 0.2728)** | | | |
| ≥ 1 Crystalloid bolus | 4.3 | 1.5-12.4 | **.007** |
| ISS | 1.0 | 1.0-1.1 | .715 |

**Table 3**: ICU = intensive care unit, ISS = injury severity score, *hospital stay of > 15 days is the upper 75$^{th}$ percentile for sTBI patients. Final model included all sTBI patients, n = 142. Deviance and Pearson p-values reported.

**Table 4: Demographic and clinical characteristics of sTBI patients vs. severely injured non-sTBI patients**

| | sTBI (n = 142) | No sTBI but with one other organ system AIS ≥ 3 (n=130) | p-value |
|---|---|---|---|
| **Age (years)** | 6.0 | 9.0 | **<.001** |
| **Sex (n% male)** | 78 (54.9%) | 81 (62.3%) | .217 |
| **Injury type (n% blunt)** | 131 (92.3%) | 99 (76.2%) | **<.001** |
| **Presenting GCS (median, IQR)** | 10.0 (3.0, 14.0) | 150 (14.0, 15.0) | **<.001** |
| **ISS** | 25.0 | 16.0 | **<.001** |
| **Initial hemoglobin** | 11.3 | 12.1 | **.010** |
| **Initial INR** | 1.2 | 1.2 | .156 |
| **Pre-hospital crystalloid given (n%)** | 36 (27.1%) | 29 (24.8%) | .682 |
| **Pre-hospital blood products (n%)** | 3 (2.2%) | 2 (1.7%) | 1 .00 |
| **Blood product transfusion within 30-hours of injury (n%)** | 63 (44.4%) | 50 (38.5%) | .324 |
| **Blood received first (n%)** | 20 (31.7%) | 26 (52.0%) | **.030** |
| **≥ 1 crystalloid bolus (n%)** | 75 (52.8%) | 61 (46.9%) | .332 |
| **ICU admission (n%)** | 112 (78.9%) | 78 (60.0%) | **< .001** |
| **ICU days** | 5 | 3 | **.031** |
| **Mechanical ventilation (n%)** | 84 (59.2%) | 42 (32.3%) | **< .001** |
| **Ventilator days** | 4.0 | 2.5 | **.022** |
| **Any complication (n%)** | 28 (19.7%) | 12 (9.2%) | **.032** |
| **Pneumonia** | 5 (3.5%) | 0 (0.0%) | .061 |
| **Re-intubation** | 3 (2.1%) | 1 (0.8%) | .624 |
| **ALI/ARDS** | 1 (0.7%) | 1 (0.8%) | 1.00 |
| **DVT or PE** | 3 (2.1%) | 3 (2.3%) | 1.00 |
| **Blood Stream Infection** | 1 (0.7%) | 1 (0.8%) | 1.00 |
| **UTI** | 1 (0.7%) | 0 (0.0%) | 1.00 |
| **Sepsis** | 1 (0.7%) | 1 (0.8%) | 1.00 |

| | | | |
|---|---|---|---|
| **Other Complication** | 13 (9.2%) | 5 (3.8%) | .079 |
| **In-hospital mortality (n%)** | 20 (14.1%) | 3 (2.3%) | **<.001** |

**Table 4:** Results presented as medians or n (%) unless otherwise specified. GCS = Glasgow coma score, ISS = injury severity score, INR = international normalized ratio, ICU = intensive care unit, ALI/ARDS = acute lung injury or acute respiratory distress syndrome, DVT or PE = deep vein thrombosis or pulmonary embolism.

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 | Title Page |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 6 | Abstract Page |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 7 | Intro: Para 1, lines 2-10 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 7-8 | Intro: lines 24-29 |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 8 | Methods: Para 1, Lines 7-10 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 8 | Methods: Para 1, Lines 7-18 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 8-9 | Methods: Para 2, Lines 21-26 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the | | |

| | | | | |
|---|---|---|---|---|
| | | number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 9 | Methods: Para 2, lines 2-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8 | Methods: para 2, lines 21-25 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 9 | Methods: para 2, lines 2-7 |
| Study size | 10 | Explain how the study size was arrived at | 8 | Methods: para 1, lines 7-10 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9 | Methods: para 3, Lines 10-17 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 9 | Methods: para 3, Lines 10-17 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 9 | Methods: para 3, Lines 10-17 |
| | | (*c*) Explain how missing data were addressed | 9 | Methods: para 3, Lines 10-17 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | | |
| | | (*e*) Describe any sensitivity analyses | n/a | |
| **Results** | | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 9 | Results: para 1, lines 21-23 |
| | | (b) Give reasons for non-participation at each stage | | |

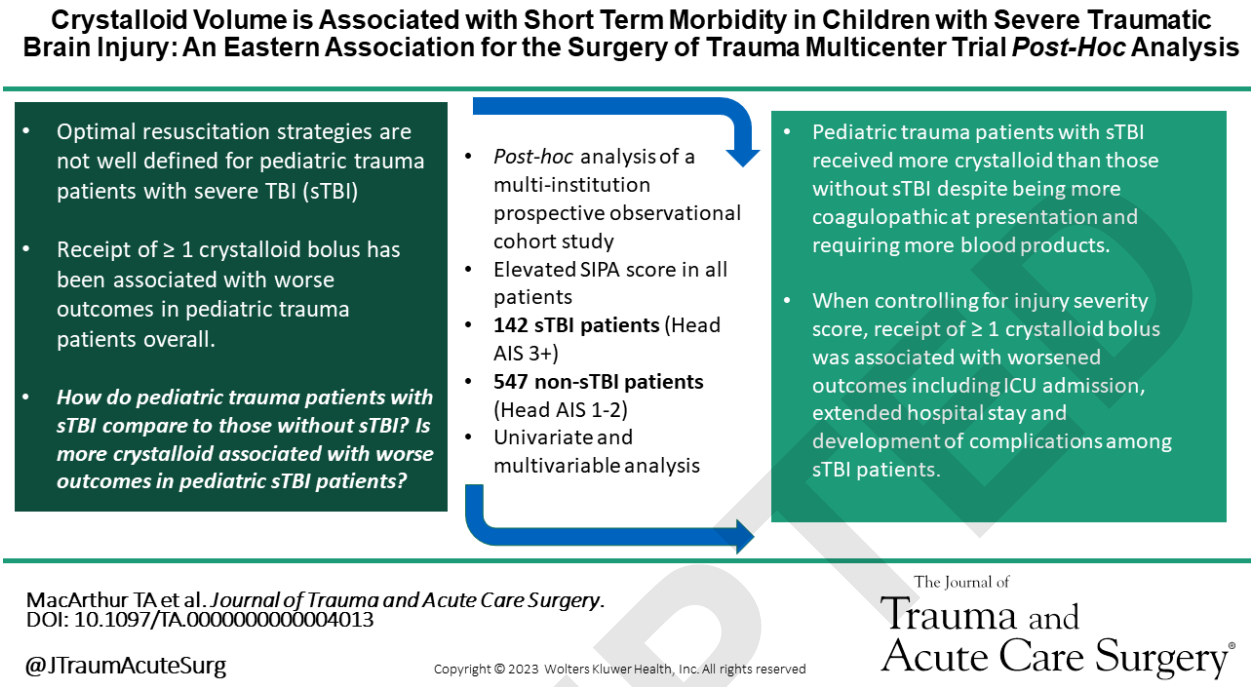
| | | | | |
|---|---|---|---|---|
| | | (c) Consider use of a flow diagram | | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9-10 | Results: para 1, lines 21-28 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 13 | Results: Para 7, lines 6-11 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 8 | Methods: para 2, line 22-23 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 9 | Results: para 1, lines 21-23 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 11 | Results: para 5, lines 11-17 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 9 | Methods: para 3, Lines 10-17 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n/a | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 10-14 | Multiple subanalysis broken down in results section: paragraphs 2-5 |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14-15 | Discussion: para 1, lines 16-19 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 16 | Discussion: para 5, lines 1-9 |

| | | | | |
|---|---|---|---|---|
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16 | Conclusion: para 1, lines 12-16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16 | Discussion: para 5, lines 4-6 |
| **Other information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 4 | Title page, funding section |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Visual Abstract




MacArthur TA et al. *Journal of Trauma and Acute Care Surgery*.
DOI: 10.1097/TA.0000000000004013

@JTraumAcuteSurg



The Journal of Trauma and Acute Care Surgery®