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OUTCOMES FOLLOWING CONCOMITANT TRAUMATIC BRAIN INJURY AND HEMORRHAGIC SHOCK: A SECONDARY ANALYSIS FROM THE PROPPR TRIAL

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Abstract

Background—Often the clinician is faced with a diagnostic and therapeutic dilemma in patients with concomitant traumatic brain injury (TBI) and hemorrhagic shock (HS), as rapid deterioration from either can be fatal. Knowledge about outcomes following concomitant TBI and HS may help prioritize the emergent management of these patients. We hypothesized that patients with concomitant TBI and HS (TBI+HS) had worse outcomes and required more intensive care compared to patients with only one of these injuries.

Methods—This is a post-hoc analysis of the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. TBI was defined by a head abbreviated injury scale >2. HS was

defined as a base excess ≤ -4 and/or shock index ≥ 0.9 . The primary outcome for this analysis was mortality at 30 days. Logistic regression, using generalized estimating equations (GEE), was used to model categorical outcomes.

Results—670 patients were included. Patients with TBI+HS had significantly higher lactate (median 6.3; IQR 4.7,9.2) compared to the TBI group (median 3.3; IQR 2.3,4). TBI+HS patients had higher activated prothrombin times and lower platelet counts. Unadjusted mortality was higher in the TBI+HS (51.6%) and TBI (50%) groups compared to the HS (17.5%) and neither group (7.7%). Adjusted odds of death in the TBI and TBI+HS groups were 8.2 (95% CI, 3.4–19.5) and 10.6 (95% CI, 4.8–23.2) times higher, respectively. Ventilator, ICU- and hospital-free days were lower in the TBI and TBI+HS groups compared to the other groups. Patients with TBI+HS or TBI had significantly greater odds of developing a respiratory complication compared to the neither group.

Conclusions—The addition of TBI to HS is associated with worse coagulopathy prior to resuscitation, and increased mortality. When controlling for multiple known confounders, the diagnosis of TBI alone or TBI+HS was associated with significantly greater odds of developing respiratory complications.

Keywords

traumatic brain injury; hemorrhagic shock; resuscitation; trauma

BACKGROUND

Despite advances in trauma resuscitation over the past two decades, hemorrhage and traumatic brain injury (TBI) remain leading causes of death in both civilian and military populations.^{1–3} TBI is the leading cause of morbidity and mortality in patients following injury, and hemorrhage is the second— and most preventable—cause of death.^{1–3} When these injuries occur concurrently, the clinician is faced with a diagnostic and therapeutic dilemma, as rapid deterioration of a patient from either TBI or hemorrhage can be lethal. There is currently a paucity of data to help guide decision-making in these circumstances, and knowledge about the physiological phenotype following concomitant TBI and hemorrhagic shock (HS) may help prioritize the emergent management of these injuries.

The contemporary damage-control resuscitation (DCR) paradigm supports actively bleeding trauma patients until hemorrhage control is achieved.^{4–7} Primary objectives include resolution of immediate life threatening injuries followed by optimization of physiological status in the perioperative period.^{4,6} The principles of DCR center on early hemorrhage control and limiting ongoing blood loss by adopting strategies that limit crystalloid fluid administration, reduce blood pressure targets, and maintain hemostasis through balanced transfusion strategies.^{4,7} A central tenet of the DCR paradigm involves early administration of blood products in a balanced ratio; the Pragmatic Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial was the first and largest prospective study to examine two different balanced blood product ratios in patients predicted to receive a massive transfusion.⁸ Application of DCR strategies has reduced mortality from HS and also seems to reduce the incidence and severity of complications such as organ failure and infection.^{5,6,9}

However, very little is known about the clinical implications of DCR for patients with TBI and HS, especially considering the coagulopathy that often accompanies TBI.^{1,10–15} Additionally, there is virtually no data on how DCR affects neurologic status and outcomes with concomitant TBI.

More research is urgently required to help guide decision-making in cases of TBI and HS. The primary objective of this post hoc study was to examine the impact of combined TBI and HS on outcomes and intensive care requirements. We hypothesized that patients with concomitant TBI and HS (TBI+HS) had worse outcomes and required more intensive care compared to patients with only one of these injuries. We also hypothesized that a high incidence of coagulopathy was present in patients with both TBI and HS.

METHODS

This is a post-hoc analysis of the Pragmatic Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial.⁸ The PROPPR trial was performed under Exception from Informed Consent (EFIC) guidelines and approved by all institutional review boards at participating hospitals as well as the US Army Human Research Protection Office, the Secretary of the Army, and the US Food and Drug Administration. The details of the PROPPR trial have been published previously.^{8,16,17} Briefly, the trial included severely injured patients predicted to receive a massive transfusion and admitted to 12 North American Level I trauma centers. Patients were randomized to a 1:1:1 ratio of plasma: platelets: red blood cells (RBC) versus a 1:1:2 ratio. In this analysis, TBI was defined by a head abbreviated injury scale >2 . HS was defined as admission base excess <-4 ^{18–21} and/or admission shock index >0.9 . Ten patients out of the original 680 were not included in this analysis because they were missing base deficit and heart rate or blood pressure values on admission. The primary outcome for this analysis was mortality at 30 days.

Differences among groups were assessed for statistical significance, and 95% confidence intervals were calculated using robust variance estimates of general estimating equations (GEE) to accommodate non-constant variance. All group comparisons were adjusted for heterogeneity. Additional analyses were conducted with adjustment for baseline covariates, including age, sex, race, ethnicity, any blunt or penetrating injury, pre-randomized total blood products, pre-randomized total crystalloids or colloids, time to randomization, and ABC score ≥ 2 . Variables with more than 10% missing were not included as covariates in the regression models. Logistic regression, using GEE to control for clustering by study center, was used to model categorical outcomes. Treatment assignment and HS/TBI group variables with a random effect for site were included in all models. Other covariates were chosen using purposeful selection and a p-value <0.10 . A GEE model with an independent correlation structure was chosen and multiple regression diagnostics were performed on the final model to assess model adequacy (i.e., goodness of fit testing, residual plots, Cook's D, and DFBETA plots). A subgroup analysis was performed modeling the Glasgow Outcome Score-Extended (GOSE) dichotomized to a variable indicating a poor outcome (i.e., a GOSE of 6 or less). Statistical analyses were performed using SAS/STAT software, Version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Demographic and physiological data are presented in Table 1. 670 patients were included. Patients in the TBI only group were the most likely to have a blunt injury and be in the 1:1:1 group compared to all other categories. There were clinically significant differences in admission vital signs among the groups. Patients with TBI+HS had the lowest median systolic blood pressure (SBP) and highest heart rate (HR) compared to all other groups. Patients with TBI+HS had higher lactate (median 6.3; interquartile range [IQR] 4.7, 9.2) compared to the TBI only group (median 3.3; IQR 2.3, 4), but not the HS only group (median 7.0; IQR 4.7, 10.7). TBI+HS patients had higher activated prothrombin times and lower platelet counts compared to all other groups at admission (Table 1). Compared to the TBI only group, patients with TBI+HS had significantly smaller median maximum amplitude and lower G-value; no other thromboelastography results were statistically different between the two groups.

Within the first 24 hours, patients in the TBI+HS group received more total RBCs, more FFP, and more platelets compared to all other groups (Figure 1). The total volume of crystalloids, colloids, and tranexamic acid did not differ between groups. Significantly more patients in the TBI+HS group required a massive transfusion, defined as 10 units of RBCs within 24 hours, (60%) compared to all other groups ($p < 0.001$). However the critical administration threshold (CAT), which is defined as 3 units of blood products within 1 hour and is less affected by survivor bias than MT, was not significantly different among the four groups ($p = 0.21$). Time to hemostasis was longer in both the HS only group and the TBI+HS group compared to the other groups. Fewer patients in the TBI+HS group achieved hemostasis (76.6%) compared to all other groups, although this result was not statistically significant ($P = 0.09$).

Hospital-free, ICU free and ventilator-free days were lower in the TBI only and TBI+HS groups compared to the other groups (Table 2). Significantly fewer TBI and TBI+HS patients were discharged home and both groups had a higher proportion of multiple organ failure as compared to the other groups. Unadjusted mortality was higher in the TBI+HS and TBI only groups.

In the adjusted analysis of 30 day mortality, odds of death in the HS only, TBI only and TBI+HS groups were 2.6 (95% CI, 1.2–5.4), 8.2 (95% CI, 3.4–19.5) and 10.6 (95% CI, 4.8–23.2) times higher than the neither group, respectively. Covariates in this model included treatment group, age, blunt injury, total blood products received prior to randomization and time to randomization. Using multiple logistic regression and excluding early deaths (<24 hours) because they were not at risk of developing a respiratory complication, patients in the TBI only and HS+TBI groups had significantly increased odds of developing a respiratory complication (acute respiratory distress syndrome, acute lung injury, or ventilator-associated pneumonia) compared to the neither group. Adjusted odds of developing a respiratory complication were 4.6 (95% CI, 1.6–13.1) and 2.9 (95% CI, 1.9–4.3) in the TBI only and HS+TBI groups respectively. The HS only group did not have significantly increased odds of respiratory complications compared to the neither group (OR 1.4; 95% CI, 0.89–2.19). This model adjusted for treatment group, sex, race, blunt injury, and time to randomization.

One hundred nineteen patients had information regarding the Glasgow Outcomes Scale Extended (GOSE). Unadjusted differences in GOSE were not statistically significantly different between the TBI only group (median GOSE 1.0: IQR; 2,4) and the TBI+HS group (median GOSE 1: IQR; 1,4). In the final logistic regression model, treatment with a 1:1:1 ratio was associated with an increased odds of having a worse GOSE (OR 1.92: 95% CI; 1.11, 3.31), but time to randomization was associated with an improved GOSE (OR 0.97: 95% CI; 0.96,0.98); no other variables were independently associated with worse neurological outcomes as assessed by GOSE.

DISCUSSION

TBI and HS remain the predominant predictors of death following severe injury. The combination of TBI and HS is associated with worse coagulopathy prior to resuscitation and increased morbidity and mortality compared to the HS or neither groups. When controlling for multiple known confounders, the diagnosis of TBI alone or TBI+HS was associated with significantly greater odds of developing respiratory complications.

The worse outcomes observed in the TBI+HS group are not surprising considering well-established principles of pathophysiology. In models of penetrating brain injury and HS, regional cerebral blood flow has been shown to decrease by more than 70% from baseline and is associated with slower cortical spreading depolarizations and reductions in brain tissue oxygen tension (P(bt)O₂).²² Combined hypoxemia and hemorrhagic shock in animal models of TBI + HS have been associated with transient intracerebral reductions in brain glucose, pyruvate, and prolonged elevations of lactate.^{23,24} Energy-related neurochemical dysregulation in TBI + HS is likely a major factor contributing to worse neurologic outcomes.²⁵ Therefore, principles of damage-control resuscitation, which include permissive hypotension,^{4,5,9} require further study in patients with TBI+HS, since a higher mean arterial pressure (>70-mm Hg) may result in better cerebral blood flow and cerebral mitochondrial function.²⁶ Speed of resuscitation may also be imperative for protecting brain function; animal models using a stepwise ratio-guided protocol with FFP (compared to a bolus protocol) have demonstrated a neuroprotective effect.²⁷ Additional pharmacologic modalities, such as valproic acid^{28,29} and hypertonic saline³⁰ continue to be studied for the prevention of cerebral metabolic derangements and excitotoxicity in patients with TBI + HS.

In this analysis, patients with concomitant TBI and HS had worse coagulopathy, as evidenced by higher activated prothrombin times and lower platelet counts compared to all other groups at admission and upon termination of the study protocol. This finding is of great importance for trauma surgeons, intensivists, and all providers charged with caring for patients with these injuries. Whereas brain injury has been shown to cause altered vascular compensation in response to HS,³¹ questions remain about the relationship between coagulopathy and the size of brain lesions.^{15,22,30,32,33} Ratio-guided resuscitation with fresh frozen plasma (FFP) may have beneficial effects for patients with TBI + HS,¹⁵ including fewer inflammatory complications.^{5,6,9} In experimental large animal studies, early administration of FFP reduced the size of brain lesions, decreased cerebral edema, and substantially attenuated the degree of neurological impairment.^{32,34} Benefits of FFP resuscitation may be related to gene expression. Recent work has shown that FFP

resuscitation was positively associated with two distinct gene clusters, with up-regulation of genes involved in metabolic and platelet signaling as well as collagen formation, and down regulation of inflammatory pathway genes.³⁵ Further work in this area is indicated to define the pathophysiological consequences of TBI + HS in humans, and the effects of interventions, such as ratio-guided resuscitation with blood components.

The presence of TBI only and TBI + HS was associated with greater odds of developing respiratory complications. This finding has significant implications for perioperative care of these patients. Pulmonary complications are known to be prevalent in patients with TBI. Acute lung injury, acute respiratory distress syndrome, pneumonia, pleural effusions, pulmonary edema, and pulmonary emboli are frequently encountered in this population.³⁶ Timing of tracheostomy,³⁷ early application of early lung protective strategies,³⁸ and timely mobilization³⁹ merit special consideration in this population.

There are a number of limitations with this work. Most studies of TBI and HS have been focused on neuronal death,³³ neurochemical changes,²³ or other physiological mechanisms,^{22,24} and none have been done in humans. While the number of patients in this post hoc analysis of patients previously randomized in PROPPR yielded a modest number of patients with TBI and HS, to our knowledge, this represents the largest study population with these two conditions conducted to date. The patients enrolled in PROPPR were selected because they were thought to be massively bleeding by the Assessment of Blood Consumption score or physician gestalt. For this reason, the results may not be applicable to a more general population of trauma patients with HS and/or TBI.⁴⁰ Coagulopathy in this study was assessed with conventional tests such as PT, aPTT, and INR. Analyses did not fully control for additional variables such as thromboelastography since these results were not universally available for all patients in PROPPR. Although the role of thromboelastography and viscoelastic monitoring continues to evolve in trauma patients,⁴¹⁻⁴³ it is possible that the degree of coagulopathy may have been underestimated in this study population since a growing body of literature suggests that early trauma-induced coagulopathy may be detected with these methods before changes are observed with conventional coagulation tests.⁴⁴ Finally, longer term outcomes data were not available in this post hoc study; GOSE was studied in a small proportion (n=119) of patients where these data were available. Considering the relatively small number of patients with GOSE, it is difficult to draw firm conclusions regarding transfusion ratios and time to treatment. Given that this is a post hoc secondary analysis of prospectively collected data, it is impossible to make causal inferences; future work in this area, including additional multi-center studies that are appropriately powered to investigate the clinical impact of TBI with concomitant HS are warranted to elucidate physiological mechanisms and potentially beneficial resuscitation strategies.

Future studies in this area will be difficult to design and execute, but more work in this area is necessary considering the findings from our analysis. In this study, definitions of HS and TBI were based on the data available in PROPPR, which was not designed to prospectively identify these groups. In future studies, better definitions for TBI will be required. These definitions will likely require biomarkers, advanced monitors, or other biological measures of neuronal injury that can be readily measured. Future studies examining interventions for

TBI+HS will need to utilize innovative designs and methodologies such as competing risks analyses, Bayesian analyses, and adaptive trial designs; broader study endpoints will also need to be considered, including indices of morbidity.⁴⁵

CONCLUSION

The combination of TBI and HS was common (18%) and associated with worse coagulopathy prior to resuscitation, increased mortality at 30 days, and increased odds for developing a respiratory complication. Additional work is required in this area to better understand the pathophysiological consequences and potentially beneficial therapeutic interventions for patient with TBI and concomitant HS.

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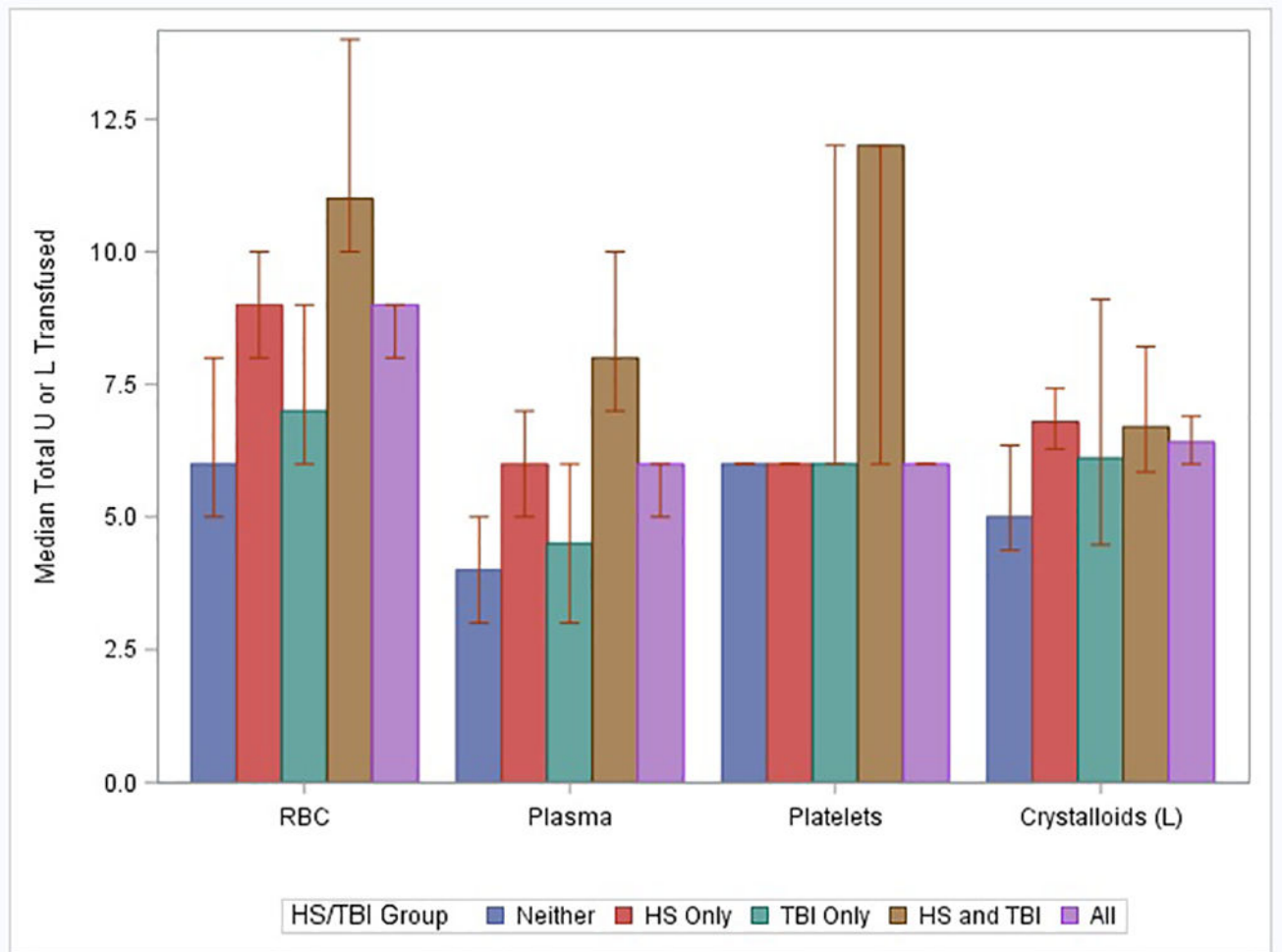


Table 1

Demographic and physiological data.

Characteristic	Neither (N=130)	HS Only (N=388)	TBI Only (N=28)	HS and TBI (N=124)	All (N=670)
Age in years	37.5 (27.51)	32 (24, 46.5)	55 (38, 69.5)	35.5 (23,56)	34.5 (25,51)
Treatment Group (%)					
1:1:1	67 (51.5)	197 (50.8)	20 (71.4)	51 (41.1)	335 (50)
1:1:2	63 (48.5)	191 (49.2)	8 (28.6)	73 (58.9)	225 (50)
Gender (%)					
Male	111 (85.4)	318 (82.0)	18 (64.3)	90 (72.6)	537 (80.1)
Female	19 (14.6)	70 (18.0)	10 (35.7)	34 (27.4)	133 (19.9)
Race (%)					
Caucasian	73 (56.2)	237 (61.1)	22 (78.6)	102 (82.3)	434 (64.8)
African American	49 (37.7)	114 (29.4)	1 (3.6)	14 (11.3)	178 (26.6)
Other Race	9 (6.9)	37 (9.5)	5 (17.9)	8 (6.5)	59 (8.8)
Mechanism of Injury					
Blunt injury only	55 (42.3)	164 (42.3)	27 (96.4)	104 (83.9)	357 (53.3)
Penetrating injury only	75 (57.7)	220 (56.7)	1 (3.6)	17 (13.7)	320 (47.8)
Both types of injury	0	5 (1.0)	0	3 (2.4)	
Systolic blood pressure	114 (88, 132)	100 (80,124)	104 (82, 131)	98 (79,123)	102 (80,126)
Heart rate	99 (82,120)	118 (98,133)	104 (80, 122)	120 (98,142)	114 (94,132)
Respiratory rate	20 (16,26)	22 (18,28)	20 (16,5,22)	20 (16,24)	20 (17,26)
Glasgow Coma Scale	15 (13,15)	14 (5.5,15)	3 (3,11.5)	3 (3,8)	14 (3,15)
Head AIS scores	0	0	5 (2,5,5)	4 (3,5)	0 (0,2)
Prehospital intubation (%)	20 (15.4)	74 (19.1)	13 (46.4)	72 (58.1)	179 (26.7)
pH (median, IQR)	7.3 (7.3, 7.4)	7.2 (7.1,7.3)	7.3 (7.3,7.4)	7.2 (7.0,7.3)	7.2 (7.1,7.3)

Characteristic	Neither (N=130)	HS Only (N=388)	TBI Only (N=28)	HS and TBI (N=124)	All (N=670)
Base excess	-1.5 (-3.1, 1.1)	-10 (-14.3, -6.8)	-1 (-2.4, 1.2)	-10.4 (-14, -7.6)	-8 (-12.7, -4)
Lactate	3.4 (2.5, 5.1)	7 (4.7, 10.7)	3.3 (2.3, 4.0)	6.3 (4.7, 9.2)	6 (3.7, 9.2)
Hematocrit	37 (33.2, 41.6)	34.7 (29.1, 39.4)	34.2 (28.5, 40.8)	34.1 (30.5, 38.6)	35 (30.4, 39.5)
PT	14.8 (13.9, 16.1)	15.6 (14.4, 17.3)	15.3 (14.9, 17)	17.6 (15.7, 20.2)	15.7 (14.5, 17.6)
aPTT	27 (24, 30.3)	28.6 (25.4, 33.8)	32 (29, 40)	38.9 (30.4, 53)	29.6 (25.5, 35.5)
INR	1.2 (1.1, 1.3)	1.3 (1.2, 1.5)	1.3 (1.2, 1.6)	1.5 (1.3, 1.7)	1.3 (1.2, 1.5)
Thromboelastography results*					
R-time (minutes)	3.3 (2.7, 4.2)	3.8 (2.8, 4.7)	3.6 (3.4, 4)	4.2 (3.2, 5)	3.8 (2.9, 4.7)
K-time (minutes)	1.3 (1.1, 1.7)	1.4 (1.2, 1.8)	1.4 (1.2, 2.2)	1.8 (1.3, 2.5)	1.5 (1.2, 1.9)
Alpha angle (%)	72.4 (67.4, 75.3)	70.7 (65.7, 74.3)	68.3 (61.3, 73.4)	65.1 (59, 70.4)	70.2 (64.2, 74.3)
Maximum amplitude (mm)	61.2 (56, 65.4)	61.5 (55.4, 66)	61.2 (57.8, 66.8)	57.3 (46.3, 63.1)	60.8 (54.2, 65.4)
G-value (d/sc)	7.9 (6.4, 9.5)	8 (6.3, 9.7)	7.9 (6.8, 10)	6.7 (4.3, 8.6)	7.8 (5.9, 9.4)
Ly30 (%)	0.6 (0, 1.9)	0.3 (0, 1.9)	0.1 (0, 1)	0.7 (0, 8)	0.3 (0, 2.2)

* Thromboelastography data were not available for all patients. Data are presented as medians with an interquartile range (P25, P75).

Table 2

Unadjusted outcomes and transfusion data.

Outcome	Neither (N=130)	HS Only (N=388)	TBI Only (N=28)	TBI + HS (N=124)	All (N=670)
Hospital free days	14.5 (0,21)	7 (0,18.5)	0	0	1 (0,17)
ICU free days	25 (15,28)	22 (2,26)	0 (0,12)	0 (0,14)	18 (0,26)
Ventilator free days	28 (21,29)	26 (7,28)	0 (0,14.5)	0 (0,16)	24 (0,28)
Discharge GCS	15 (15,15)	15 (15,15)	9.5 (8,13)	14 (11,15)	15 (15,15)
Discharge GOSE	6 (4,8)	5 (3,7)	1 (1,2)	1 (1,3)	1 (1,4)
Disposition at 30 days (%)					
Hospitalized	23 (17.7)	95 (24.5)	7 (25)	34 (27.4)	159 (23.7)
Home	61 (46.9)	153 (39.4)	2 (7.1)	5 (4)	221 (33)
Long-term care facility	3 (2.3)	4 (1)	3 (10.7)	6 (4.8)	16 (2.4)
Skilled nursing facility	7 (5.4)	17 (4.4)	0	2 (1.6)	26 (3.9)
Rehabilitation facility	14 (10.8)	19 (4.9)	2 (7.1)	10 (8.1)	45 (6.7)
Acute care hospital	2 (1.5)	7 (1.8)	0	2 (1.6)	11 (1.6)
Other	10 (7.7)	25 (6.4)	0	1 (0.8)	36 (5.4)
Died	10 (7.7)	68 (17.5)	14 (50)	64 (51.6)	156 (23.3)
Multiple organ failure (%)	2 (1.5)	7 (1.8)	2 (7.1)	6 (4.8)	17 (2.5)
Transfusion data					
Total RBCs	6 (4,10)	9 (6,15)	7 (5,11.5)	11 (7,18.5)	9 (6,15)
Total Plasma	4 (2,8)	6 (3,12)	4.5 (3,8)	8 (4,13)	6 (3,11)
Total Platelets	6 (0,12)	6 (6,18)	6 (6,12)	12 (6,18)	6 (6,18)
Total Crystallloids	5 (3,4,8.5)	6.8 (4,10.5)	6.1 (3.6, 9.3)	6.7 (3.7,10.4)	6.4 (3.7, 9.9)
Massive transfusion (%)	39 (30)	186 (47.9)	8 (28.6)	75 (60.5)	308 (46)

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Outcome	Neither (N=130)	HS Only (N=388)	TBI Only (N=28)	TBI + HS (N=124)	All (N=670)
Time to anatomic hemostasis from randomization (minutes)	86 (42,155)	110 (62.5,180)	93 (61,163)	115 (72,252)	103 (61,179)

Continuous data are described with median and interquartile range. GCS-Glasgow coma scale, GOSE-Glasgow outcome scale. Transfusion data includes all blood products given in the prehospital environment up to the first 24 hours after admission.