

A higher plasma to red cell ratio is associated with lower 24-hour mortality in injured children
receiving massive transfusion

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A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2020

Committee:

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Program Authorized to Offer Degree:

Epidemiology

Title and Abstract:

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Full text:

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This is a non-final version of an article published in final form in
Critical Care Medicine. 2019 Jul;47(7):975-983. doi: [10.1097/CCM.0000000000003708](https://doi.org/10.1097/CCM.0000000000003708).

University of Washington

Abstract

A higher plasma to red cell ratio is associated with lower 24-hour mortality in injured children receiving massive transfusion

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Background: Higher fresh frozen plasma (FFP) and platelet to packed red blood cell (PRBC) ratios are associated with decreased mortality in injured adults. We sought to determine if higher FFP:PRBC and platelet:PRBC ratios are associated with lower 24-hour mortality in bleeding pediatric trauma patients.

Methods: This was a retrospective cohort study using the Pediatric Trauma Quality Improvement Program Database from 2014 to 2016. Injured children (≤ 14 years) who received massive transfusion (≥ 40 mL/kg total blood products in 24 hours) were included. Multivariable Poisson regression was used to determine the association between ratios of FFP:PRBC and platelet:PRBC and 24-hour mortality.

Results: Of 123,836 patients, 590 underwent massive transfusion, of which 583 met inclusion criteria. Of included patients, 60% were male and the median age was 5 (IQR 2 to 10) years. Cohort 24-hour mortality was 19.7% (95% CI: 16.6 to 23.2%). The high ($\geq 1:1$) and medium ($\geq 1:2$ and $< 1:1$) FFP:PRBC ratio groups had a lower risk of death at 24 hours (high: aRR 0.49, 95% CI: 0.27 to 0.87; medium: aRR 0.60, 95% CI: 0.39 to 0.92) compared to the low ratio group ($< 1:2$). There was no association between platelet:PRBC ratio and mortality (aRR: 0.94, 95% CI 0.51 to 1.71).

Conclusions: Severely injured children with hemorrhage likely benefit from higher FFP:PRBC ratios. While this study is the largest study evaluating blood product ratios in pediatric trauma patients, larger prospective studies are necessary to further evaluate the optimum blood product ratios to minimize mortality in this population.

INTRODUCTION

Hemorrhage is a significant cause of preventable early trauma mortality (1-3). Damage control resuscitation, consisting of immediate hemorrhage control, limited intravenous crystalloid, early warmed blood products, balanced massive transfusion, and permissive hypotension is a mainstay of traumatic hemorrhage management in both adults and children (1, 4, 5). However, there is minimal evidence supporting these interventions in children (6-8). There is evidence supporting balanced massive transfusion of adults in traumatic hemorrhagic shock with a ratio of 1:1:1 of fresh frozen plasma (FFP): platelets: packed red blood cells (PRBC) (9-11), but balanced massive transfusion protocols have been instituted in many pediatric trauma centers without definitive supporting evidence (1, 3, 12-15).

Two studies evaluated the effect of balanced transfusion on in-hospital mortality in pediatric trauma patients in a combat setting (12, 13). Edwards *et al* evaluated 224 injured children in the Department of Defense trauma registry from 2002-2012 who received high-volume transfusions (13). Cannon *et al* performed a similar study evaluating 364 injured children in the Department of Defense trauma registry from 2001-2013 who received massive transfusion or who died in the first 24h and received a blood transfusion. In both studies, there was no significant difference in in-hospital mortality by FFP:PRBC ratio. These studies have limited generalizability to the civilian population, as less than 15% of the evaluated children had injuries due to blunt trauma. A few additional single-center civilian studies have not shown an association between mortality and FFP:PRBC transfusion ratio. These studies are limited by small sample sizes and single institution experience (3, 14, 16).

In this study, we evaluated a large cohort of civilian pediatric trauma patients requiring massive transfusion. The primary objective was to determine if there is an association between higher FFP:PRBC and platelet:PRBC ratios and lower mortality in pediatric trauma patients requiring massive transfusion.

METHODS

Data Source

The Pediatric Trauma Quality Improvement (TQIP) database is a national database including approximately 120,000 injured pediatric patients from 71 participating facilities (level I or II American College of Surgeons or state designated pediatric trauma centers). Patients included in the database are those under 18 years who sustained a traumatic injury and were either admitted to the trauma facility or died while at the facility. The TQIP database was chosen because it includes specific transfusion volumes at two time points (4h and 24h). Per the University of Washington IRB, the study did not constitute human subjects research and therefore did not require review.

Study Population

The study population consisted of pediatric trauma patients (≤ 14 years old) receiving massive transfusion as documented in the pediatric TQIP database from 2014-2016. Massive transfusion was defined as ≥ 40 mL/kg of total blood products within the first 24h (17). Patients were excluded if they had a non-traumatic mechanism or an unknown outcome. To mitigate survival bias, patients who died within the first 30 minutes of arrival were excluded, thus removing those patients with a low FFP:PRBC ratio due to inadequate time to receive FFP. Patients who did not receive any PRBC were also excluded, because the primary independent variables could not be calculated due to division by zero.

Outcome measures and predictor variables

Data on demographics, injury characteristics, emergency department (ED) vital signs, facility characteristics, blood product administration, hemorrhage management, disposition, and complications were retrieved for each patient. The primary independent variables were FFP:PRBC ratio and platelet:PRBC ratio. Facilities report either number of units or volume of transfusion for each type of blood product given in the first 4h and 24h, along with the volume which constitutes a unit of each product type at their hospital. The volumes per kilogram body weight of each type of blood product and in total were calculated. Standardized units of platelets were back-calculated from reported volumes and units using a volume of 250 mL (approximate volume of a 6-pack of pooled donor units) in order to account for facility variation in use of apheresis or pooled donor platelets. The FFP:PRBC and platelet:PRBC ratios were calculated by dividing the number of units of FFP or platelets by the number of units of PRBC.

The primary outcome was 24h mortality. After 24h, the primary causes of death shift from hemorrhage to traumatic brain injury (TBI), organ failure, and infection (18). Therefore in order to focus primarily on patients who would benefit from improved management of hemorrhage, we used 24h mortality as the primary endpoint. Secondary outcomes included in-hospital mortality and a predetermined list of complications. Hospital length of stay, intensive care unit (ICU) length of stay, ventilator days, and hospital disposition were evaluated for surviving patients.

Statistical analysis

The patients were divided into three groups based on their FFP:PRBC ratio at 24h: low ($<1:2$), medium ($\geq 1:2$ and $<1:1$) and high ($\geq 1:1$), and into three groups based on their platelet:PRBC ratio at 24h: none (0), low (>0 and $<1:2$), and high ($\geq 1:2$). The FFP:PRBC groups were chosen based on clinically relevant cut points (11, 15, 19). The platelet:PRBC groups were modified

slightly due to the low rate of platelet transfusion overall. Descriptive statistics were used to characterize each group. Age specific criteria were used to determine if vital signs were abnormal (20). We used multiple imputation using chained equations to account for missing values in covariates (21). Of 583 patients, at least one variable was missing in 44 (7.5%). Data was assessed for patterns of missingness and assumed to be missing at random. Ten multiply imputed data sets were created. Multivariable Poisson or logistic regression was performed to determine the association of the FFP:PRBC ratio and platelet:PRBC ratio with mortality and predetermined secondary outcomes. Covariates to adjust for mortality risk were chosen based on Haider *et al*'s optimized mortality risk adjustment model for the NTDB database in severely injured trauma patients and included: age, hypotension on arrival to the ED, mechanism of injury, total Glasgow Coma Scale (GCS), Injury Severity Score (ISS), and need for mechanical ventilation (22). Additional covariates included transfer to the trauma center, total volume of blood products per kg of body weight, and the two independent variables of interest: FFP:PRBC ratio and platelet:PRBC ratio. Separate regression models were performed to assess FFP:PRBC and platelet:PRBC ratios as continuous variables and categorical variables. In addition, separate models were performed with 4h and 24h blood product ratios.

To evaluate the effect of severe TBI and transfer patients, sensitivity analyses were planned to exclude patients with severe TBI and transfer patients, respectively. In order to evaluate the possible effect of survival bias, two additional sensitivity analyses were planned: (1) patients who did not meet massive transfusion threshold, but who received any PRBC and died within the first 24h were included; and in a separate analysis, (2) all patients who died within the first 4h were excluded. By including patients who did not meet massive transfusion threshold, we reduced the risk of excluding patients who would have met the threshold had they survived long

enough. By evaluating only patients who survived greater than 4h, we reduce the risk of including patients with falsely low FFP:PRBC ratios due to delayed administration of FFP.

Level of significance was set to $\alpha=0.05$. Assessment of secondary outcomes was considered exploratory and thus no correction for multiple comparisons was made. All hypothesis tests were two-sided. STATA/SE version 14 was used for all data analysis (StataCorp LP, College Station, TX).

RESULTS

From 2014 to 2016, 123,836 children were included in the pediatric TQIP database. As shown in Figure 1, 590 received ≥ 40 mL/kg total blood products in 24h. Seven patients were excluded due to unknown outcome or lack of PRBC transfusion, leaving a cohort of 583 massively transfused injured children.

Table 1 shows demographic and injury characteristics. When divided into three groups by FFP:PRBC ratio, patient and injury characteristics were similar. When grouped by platelet:PRBC ratio, the cohorts differed. The low platelet:PRBC group (>0 and $<1:2$) tended to be older, more severely injured, and had a higher rate of penetrating trauma.

Overall, patients received a median of 75 mL/kg (IQR: 52 to 120) total blood products in 24h (Table 2). The rate of platelet and cryoprecipitate transfusion was low (only 61% and 32% by 24h, respectively). Supplemental Figure 1 shows the distribution of FFP:PRBC and platelet:PRBC ratios at 4h and 24h.

Mortality at 24h was 19.7% (95% CI: 16.6 to 23.2%) and in-hospital mortality was 42.4% (95% CI: 38.3 to 46.5%) (Supplemental Table 1). The rate of any complication was low at 15.6%. The most common complication was deep vein thrombosis (DVT) (n=25, 4%), followed by pneumonia (n=20, 3%). There were no transfusion reactions. Among survivors, median hospital length of stay was 20 (IQR: 12 to 30) days and median ICU length of stay was 12 (IQR: 6 to 19) days.

Multivariable Poisson regression analysis revealed that both higher 4h and 24h FFP:PRBC ratios were associated with lower risk of death at 24h (aRR 0.47, 95% CI: 0.28 to 0.80 and aRR 0.42,

95% CI: 0.25 to 0.71, respectively) (Table 3). There was no association between the 4h or 24h platelet:PRBC ratio as a continuous variable and 24h mortality. Evaluating 24h FFP:PRBC ratio as a categorical variable revealed a 51% (aRR 0.49, 95% CI: 0.27 to 0.87) and 40% (aRR 0.60, 95% CI: 0.39 to 0.92) lower risk of death at 24h for the high and medium FFP:PRBC groups, respectively, compared to the low ratio group. The 4h high FFP:PRBC ratio group had a 52% (aRR 0.48, 95% CI: 0.26-0.88) lower risk of death at 24h compared to the low group. In evaluating the platelet:PRBC ratio as a categorical variable, the low 4h platelet:PRBC group had an 81% (aRR 1.81, 95% CI:1.11 to 2.94) higher risk of 24h mortality compared to those who received no platelets by 4h. There was no significant difference in mortality risk among the 24h platelet:PRBC ratio groups.

When evaluating secondary outcomes, higher FFP:PRBC ratio remained associated with lower risk of in-hospital mortality and platelet:PRBC ratio was not associated with in-hospital mortality (Table 4). There was no difference in risk of complications, except higher FFP:PRBC ratio was associated with an increased risk of DVT and higher platelet:PRBC ratio was associated with an increased risk of pneumonia. In order to further evaluate the association between FFP:PRBC ratio and risk of DVT, an exploratory post hoc analysis was performed to determine the ratio level at which the risk increased. There was no difference in risk of DVT when comparing the three predetermined FFP:PRBC groups. However, patients with FFP:PRBC ratio $\geq 2:1$ (n=16) had a 592% (aRR 6.9, 95% CI: 1.8 to 26.3) higher risk of DVT compared to those who had $< 2:1$ FFP:PRBC ratio. A post-hoc analysis of association between platelet:PRBC ratio and risk of pneumonia revealed no difference in risk of pneumonia when comparing the three predetermined platelet:PRBC groups. However, patients with platelet:PRBC $\geq 2:1$ (n=3) had an increased risk of pneumonia (aRR 23.6, 95% CI: 2.2 to 249) compared to those with a ratio $< 2:1$.

In sensitivity analyses, the association of FFP:PRBC ratio with 24h mortality remained significant in the subset of 166 patients without severe TBI (aRR 0.09, 95% CI: 0.01 to 0.63). When excluding transferred patients (n=348), FFP:PRBC ratio remained associated with mortality (aRR 0.26, 95% CI 0.12 to 0.56). When including patients who died within the first 24h and received any amount of PRBC (n=635), and when excluding those patients who died within the first 4h (n=541), the FFP:PRBC ratio remained significantly associated with mortality (aRR 0.32, 95% CI 0.20 to 0.51 and aRR 0.33, 95% CI 0.16 to 0.67, respectively).

DISCUSSION

The primary objective of this study was to determine if blood component ratios were associated with mortality in injured pediatric patients receiving massive transfusion. Our findings suggest that higher FFP:PRBC ratios, particularly greater than or equal to 1:2, are associated with lower mortality at 24h. Physiologically, patients in hemorrhagic shock are bleeding whole blood, made up of red blood cells, coagulation factors and platelets. Higher ratios of FFP:PRBC and platelet:PRBC better approximate whole blood, allowing for correction of acute traumatic coagulopathy, achievement of hemostasis, and fewer deaths from exsanguination (11). This is the largest study of massive transfusion in pediatric trauma, and the first to demonstrate a mortality benefit associated with higher FFP:PRBC ratios in children. Strengths of this study include: use of the highest quality data currently available, use of multiple imputation to account for missing data, and generalizability to level I and II trauma centers caring for injured children.

Our results contrast with prior studies which did not show an association of FFP:PRBC ratio with mortality in children (3, 12-14, 16). This may be due to the difference in primary end point from in-hospital mortality to 24h mortality (18). However, our study also showed an association between higher FFP:PRBC ratios and decreased in-hospital mortality. Previous studies were likely underpowered to detect a difference in mortality. Another possible explanation for a difference in findings compared to prior work is variation in the populations studied. The two largest previous studies included patients from the Department of Defense registry (12, 13), which had a higher rate of penetrating and blast injuries compared to this study (90% vs. 18%). In addition, as clearly stated by the authors, the data came from children who were civilian combat casualties, a situation in which not only the forces and mechanisms of injury are vastly

different from domestic civilian trauma, but so are pre-hospital care and transport times, all of which have an effect on survival in critical bleeding (23, 24). Also, massive transfusion was variously defined as ≥ 40 mL/kg of PRBC or whole blood or total blood products, ≥ 70 or 80 mL/kg of total blood products, or greater than 50% of total blood volume in previous studies. In our study, we used the standardized definition of massive transfusion in pediatric patients as ≥ 40 mL/kg of total blood products (17). Additionally, one study excluded patients with severe TBI (12). We included patients with TBI, given that the majority of our patients were multiply injured blunt trauma patients, as opposed to isolated, penetrating head trauma in the military population. We performed a sensitivity analysis evaluating those patients without severe head injury, which demonstrated an even stronger association between FFP:PRBC ratio and 24h mortality.

This study did not find a significant association between 24h platelet:PRBC ratio and 24h mortality after adjustment for injury severity, similar to two prior studies (14, 16). However, the overall rate of platelet transfusion was low and only 72 patients had a platelet ratio of $\geq 1:2$, and only 14 patients had a ratio of $\geq 1:1$. The risk of a type II error is high and further study in a prospective cohort, specifically powered to evaluate this relationship is warranted. We found an increased risk of 24h mortality in the low (>0 and $<1:2$) platelet:PRBC group at 4h compared to the group who received no platelets. The low platelet group was more severely injured than the other two platelet groups, and our model may have inadequately adjusted for the differences in patient characteristics.

The overall complication rate was low, which limits our analysis of differences in complication rate between the groups. We found an association between higher FFP:PRBC ratios and risk of

DVT. Upon further post-hoc analysis, only patients with a ratio of greater than 2:1 had this increased risk. Transfusion has been shown to be an independent risk factor for development of DVT in the pediatric trauma population (25). However, there is no evidence evaluating the effect of type of blood product transfused on risk of DVT in injured patients. Any future studies evaluating transfusion ratios should specifically evaluate risk of DVT in the analysis.

Additionally, patients with a platelet:PRBC ratio greater than 2:1 had a higher risk of pneumonia. Due to multiple secondary outcomes, there is a risk of a type I error due to multiple comparisons. We did not use the Bonferroni correction because these were exploratory analyses. We do not know of a physiologic reason for higher risk of pneumonia with higher platelet:PRBC ratio; however, future studies should specifically assess the rate of pneumonia to determine if a true relationship exists.

Survival bias is a potential limitation to this study (26). One risk is that those patients who did not survive long enough to meet the massive transfusion volume cutoff are not included. We chose to include only patients who received massive transfusion, because patients who received less than massive transfusion cannot be assumed to be in hemorrhagic shock. By including those patients who received some blood, but did not meet massive transfusion threshold, the cohort may be diluted by patients who died from non-hemorrhagic causes, such as severe TBI.

However, we performed a sensitivity analysis which included all patients who received at any amount of PRBC and died within the first 24h, and the association with mortality remained significant. An additional risk of survival bias is that FFP transfusion is often delayed compared to timing of PRBC administration and patients may die with an artificially low FFP:PRBC ratio. We performed a sensitivity analysis in which we excluded patients who died prior to 4h, thus allowing adequate time for stabilization of the FFP:PRBC ratio and found that a higher

FFP:PRBC ratio remained significantly associated with lower 24h mortality. Therefore, we believe the risk of survival bias meaningfully affecting our findings is low.

An additional limitation is that the TQIP database does not include laboratory data, volume of crystalloid administration, or documentation of adjunct treatments for coagulopathy such as tranexamic acid or recombinant factor VIIa. Edwards *et al* demonstrated that high crystalloid administration in massively transfused injured children was associated with higher mortality.(13) Additionally, multiple studies have demonstrated the association between abnormal INR, PT, and PTT and mortality (3, 12, 14). These represent potential confounders in our analysis that remain unaccounted for.

CONCLUSIONS

Higher FFP:PRBC ratios may result in improved survival in pediatric trauma patients with hemorrhagic shock. The effect of platelet:PRBC ratio on mortality remains unclear. We recommend maintaining higher FFP:PRBC ratios, at least 1:2, in bleeding injured children. Future prospective studies should be initiated to improve upon the above discussed limitations.

FUNDING

Elissa K. Butler was supported by the National Institutes of Health T-32 Pediatric Injury Research Training Program [5T32HD057822-09].

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Figure 1. Flow diagram of pediatric trauma patients in the 2014-2016 Trauma Quality Improvement Program database. Abbreviations: FFP, fresh frozen plasma; PRBC, packed red blood cells.

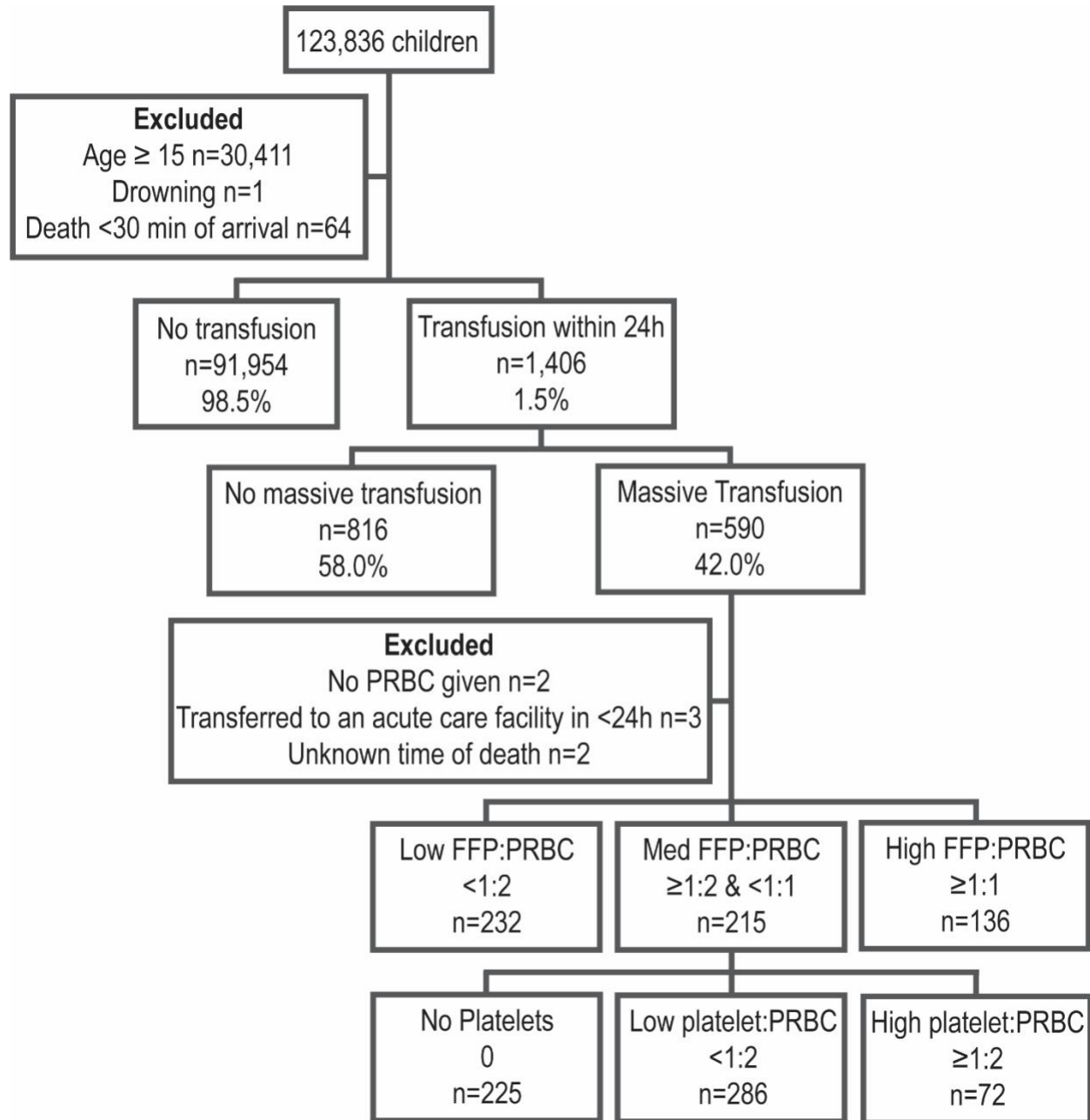


Table 1. Patient and injury characteristics of 583 pediatric trauma patients receiving massive transfusion.

Characteristic	All (n=583)	FFP:PRBC			Platelet:PRBC		
		Low <1:2 (n=232)	Med ≥1:2 & <1:1 (n=215)	High ≥1:1 (n=136)	None 0 (n=225)	Low >0 & <1:2 (n=286)	High ≥1:2 (n=72)
Age, median (IQR), y	5 (2 to 10)	4 (2 to 10)	6 (2 to 10)	5 (2 to 9)	3 (1 to 6)	7 (3 to 11)	5 (2 to 8)
Male sex, No. (%)	350 (60.0)	139 (59.9)	126 (58.6)	85 (62.5)	132 (58.7)	180 (62.9)	38 (52.8)
Dominant Injury Type, No. (%)							
Blunt	430 (73.8)	158 (68.1)	163 (75.8)	109 (80.2)	158 (70.2)	214 (74.8)	58 (80.6)
Penetrating	102 (17.5)	49 (21.1)	38 (17.7)	15 (11.0)	32 (14.2)	60 (21.0)	10 (13.9)
Other or unspecified	51 (8.8)	25 (10.8)	14 (6.5)	12 (8.9)	35 (15.6)	12 (4.2)	4 (5.6)
Mechanism, No. (%)							
Motor vehicle collision	217 (37.2)	76 (32.8)	86 (40.0)	55 (40.4)	78 (34.7)	108 (37.8)	31 (43.1)
Pedestrian	80 (13.7)	31 (13.4)	29 (13.5)	20 (14.7)	27 (12.0)	44 (15.4)	9 (12.5)
Firearm	79 (13.6)	35 (15.1)	33 (15.4)	11 (8.9)	20 (8.9)	50 (17.5)	9 (12.5)
Fall	48 (8.2)	20 (8.6)	16 (7.4)	12 (8.8)	23 (10.0)	18 (6.3)	7 (9.7)
Struck by	28 (4.8)	12 (5.2)	9 (4.2)	7 (5.2)	11 (4.9)	15 (5.2)	2 (2.8)
Stab	20 (3.4)	13 (5.6)	4 (1.9)	3 (2.2)	11 (4.9)	9 (3.2)	0 (0)
Other	111 (19.0)	45 (19.4)	38 (17.7)	28 (20.6)	55 (24.4)	42 (14.7)	14 (19.4)
ED GCS, median (IQR)^a	10 (4 to 15)	10 (5 to 15)	9 (3 to 15)	11 (4 to 15)	9 (4 to 15)	10 (4 to 15)	9 (5 to 15)
Lowest SBP hypotensive, No. (%)^b	322 (57.0)	122 (55.0)	131 (61.8)	69 (52.7)	97 (44.9)	181 (64.4)	44 (64.7)
ED heart rate, No. (%)^b							
Normal	187 (32.7)	61 (27.0)	74 (34.6)	52 (39.1)	93 (42.1)	67 (23.8)	27 (38.6)
Tachycardia	226 (39.5)	94 (41.6)	77 (36.2)	55 (41.4)	74 (33.5)	126 (44.8)	26 (37.1)
Bradycardia	159 (27.8)	71 (31.4)	62 (29.1)	26 (19.6)	54 (24.4)	88 (31.3)	17 (24.3)

Table 1. (continued)

Characteristic	All (n=583)	FFP:PRBC			Platelet:PRBC		
		Low <1:2 (n=232)	Med ≥1:2 & <1:1 (n=215)	High ≥1:1 (n=136)	None 0 (n=225)	Low >0 & <1:2 (n=286)	High ≥1:2 (n=72)
Mechanical ventilation required, No. (%)	548 (94.0)	213 (91.8)	206 (95.8)	129 (94.9)	206 (91.6)	273 (95.5)	69 (95.8)
Severe injury (AIS≥3)							
Head	417 (71.5)	162 (69.8)	155 (72.1)	100 (73.5)	161 (71.6)	200 (69.9)	56 (77.8)
Thorax	247 (42.4)	98 (42.2)	96 (44.7)	53 (39.0)	85 (37.8)	135 (47.2)	27 (37.5)
Abdomen	210 (36.0)	70 (30.2)	87 (40.5)	53 (39.0)	71 (31.6)	114 (39.9)	25 (34.7)
ISS, median (IQR)	29 (22 to 38)	27 (21 to 36)	29 (24 to 42)	29 (25 to 38)	27 (21 to 35)	30 (25 to 41)	26 (22 to 38)
Transfer from another facility, No. (%)	218 (37.5)	66 (28.5)	85 (39.7)	67 (49.3)	90 (40.0)	91 (31.9)	37 (51.4)
Hospital level, No. (%)^c							
Adult only level I or II	32 (5.5)	6 (2.6)	20 (9.3)	6 (4.4)	14 (6.2)	13 (4.6)	5 (6.9)
Adult and pediatric level I or II	275 (47.2)	92 (39.7)	101 (47.0)	82 (60.3)	115 (51.1)	124 (43.4)	36 (50.0)
Pediatric only level I or II	276 (47.3)	134 (57.8)	94 (43.7)	48 (35.3)	96 (42.7)	149 (52.1)	31 (43.1)
Management							
Angiogram only, No. (%)	34 (5.9)	14 (6.1)	17 (7.9)	3 (2.2)	10 (4.5)	22 (7.8)	2 (2.8)
Angiogram with embolization, No. (%)	17 (2.9)	5 (2.2)	7 (3.3)	5 (3.7)	4 (1.8)	11 (3.9)	2 (2.8)
Hemorrhage control procedure, No. (%)	198 (34.0)	75 (32.5)	79 (36.7)	44 (32.4)	51 (22.8)	126 (44.1)	21 (29.2)

Abbreviations: FFP, fresh frozen plasma; PRBC, packed red blood cells; IQR, interquartile range; ED, emergency department; GCS, Glasgow coma scale; SBP, systolic blood pressure; AIS, abbreviated injury score; ISS, injury severity score.

^aExcludes patients with invalid GCS due to intubation, chemical sedation or paralysis, or obstruction of the eyes (n=354).

^bAbnormal based on age specific criteria.

^cBased on American College of Surgeons or state level verification.

Table 2. Blood products received by 4h and 24h after emergency department arrival in 583 massively transfused pediatric trauma patients.^a

Blood Product	All (n=583)	FFP: PRBC	FFP:PRBC	FFP:PRBC	p
		Low <1:2 (n=232)	Med ≥1:2 & <1:1 (n=215)	High ≥1:1 (n=136)	
4 hour					
PRBC, mL/kg	37 (24 to 58)	43 (30 to 63)	40 (27 to 62)	25 (17 to 39)	<0.001
Plasma, mL/kg	15 (6 to 27)	8 (0 to 14)	20 (14 to 31)	23 (13 to 37)	<0.001
Platelets, mL/kg	0 (0 to 10)	0 (0 to 9)	3 (0 to 11)	0 (0 to 9)	0.08
Cryoprecipitate, mL/kg	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.17
Total blood products, mL/kg	57 (41 to 90)	52 (40 to 85)	66 (44 to 104)	51 (34 to 81)	<0.001
Plasma:PRBC ratio	0.50 (0.20 to 0.86)	0.20 (0 to 0.37)	0.62 (0.50 to 0.80)	1.0 (1.0 to 1.2)	<0.001
Platelet:PRBC ratio	0 (0 to 0.24)	0 (0 to 0.20)	0.11 (0 to 0.25)	0 (0 to 0.29)	0.08
24 hour					
PRBC, mL/kg	46 (32 to 71)	53 (41 to 84)	50 (33 to 80)	30 (22 to 45)	<0.001
Plasma, mL/kg	23 (13 to 36)	11 (0 to 18)	29 (19 to 43)	32 (26 to 47)	<0.001
Platelets, mL/kg	7 (0 to 15)	5 (0 to 15)	9 (0 to 17)	6 (0 to 13)	0.004
Cryoprecipitate, mL/kg	0 (0 to 2)	0 (0 to 0)	0 (0 to 3)	0 (0 to 3)	<0.001
Total blood products, mL/kg	75 (52 to 120)	70 (51 to 112)	90 (59 to 143)	70 (50 to 103)	<0.001
Plasma:PRBC ratio	0.57 (0.33 to 0.91)	0.25 (0 to 0.38)	0.67 (0.56 to 0.77)	1.1 (1.0 to 1.5)	<0.001
Platelet:PRBC ratio	0.15 (0 to 0.33)	0.09 (0 to 0.28)	0.18 (0 to 0.33)	0.17 (0 to 0.48)	0.003

Abbreviations: FFP, fresh frozen plasma; PRBC, packed red blood cells.

^aAll data presented as median (interquartile range).

Table 3. Multivariable Poisson regression analysis evaluating the association between blood component ratios and 24h mortality in 583 massively transfused pediatric trauma patients.^a

Independent Variables	aRR	95% CI
4h blood products		
Total blood products, mL/kg	1.003	1.001-1.005
FFP:PRBC ratio, continuous	0.47	0.28-0.80
Platelet:PRBC ratio, continuous	1.53	0.84-2.77
FFP:PRBC ratio, categorical		
Low <1:2	1 (Ref)	
Med ≥1:2 & <1:1	0.67	0.43-1.05
High ≥1:1	0.48	0.26-0.88
Platelet:PRBC ratio, categorical		
None 0	1 (Ref)	
Low >0 & <1:2	1.81	1.11-2.94
High ≥1:2	1.73	0.90-3.34
24h blood products		
Total blood products, mL/kg	1.002	1.000-1.004
FFP:PRBC ratio, continuous	0.42	0.25-0.71
Platelet:PRBC ratio, continuous	0.94	0.51-1.71
FFP:PRBC ratio, categorical		
Low <1:2	1 (Ref)	
Med ≥1:2 & <1:1	0.60	0.39-0.92
High ≥1:1	0.49	0.27-0.87
Platelet:PRBC ratio, categorical		
None 0	1 (Ref)	
Low >0 & <1:2	1.29	0.81-2.05
High ≥1:2	1.04	0.52-2.09

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; FFP, fresh frozen plasma; PRBC, packed red blood cells.

^aModel adjusted for age, injury mechanism, hypotension, abnormal heart rate, Glasgow coma scale, injury severity score, need for mechanical ventilation, and transfer status.

Table 4. Multivariable regression analysis evaluating secondary outcomes in 583 massively transfused pediatric trauma patients.^a

Secondary Outcomes	FFP:PRBC ratio		Platelet:PRBC ratio	
	aRR	95% CI	aRR	95% CI
Mortality				
In-hospital mortality	0.72	0.55-0.96	1.17	0.91-1.50
Complications				
Any	1.05	0.80-1.38	0.96	0.69-1.34
Deep vein thrombosis	1.77	1.22-2.57	0.17	0.02-1.30
Pneumonia	1.10	0.49-2.47	1.94	1.14-3.28
Unplanned return to operating room	1.07	0.28-4.08	1.07	0.28-4.08
Acute respiratory distress syndrome	1.29	0.69-2.41	0.34	0.02-7.24
Unplanned ICU admission or return to ICU	1.41	0.71-2.77	0.20	0.01-3.95
Acute kidney injury	0.85	0.25-2.85	1.78	0.54-5.91
Unplanned intubation	0.45	0.10-2.07	1.97	0.37-10.52
Stroke	1.44	0.67-3.08	1.11	0.31-4.03
Severe sepsis	0.24	0.02-2.83	0.96	0.19-4.82
Extremity compartment syndrome	1.19	0.45-3.16	2.64	0.09-76.0
Pulmonary embolism	0.53	0.04-7.22	1.31	0.13-13.4
Transfusion reaction ^b	1		1	
Outcomes of survivors				
Hospital length of stay	8.56	0.89-81.82		
ICU length of stay	0.84	0.18-4.03	1.92	0.05-69.53
Mechanical ventilation	1.02	0.88-1.18	0.97	0.67-1.42
Ventilator days	0.77	0.16-3.81	0.77	0.02-35.37
Disposition				
Home with or without services	1 (Ref)		1 (Ref)	
Inpatient rehabilitation	0.85	0.57-1.27	0.29	0.09-0.99
Other care facility ^c	1.44	0.91-2.29	1.26	0.41-3.93

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; FFP, fresh frozen plasma; PRBC, packed red blood cells; ICU, intensive care unit.

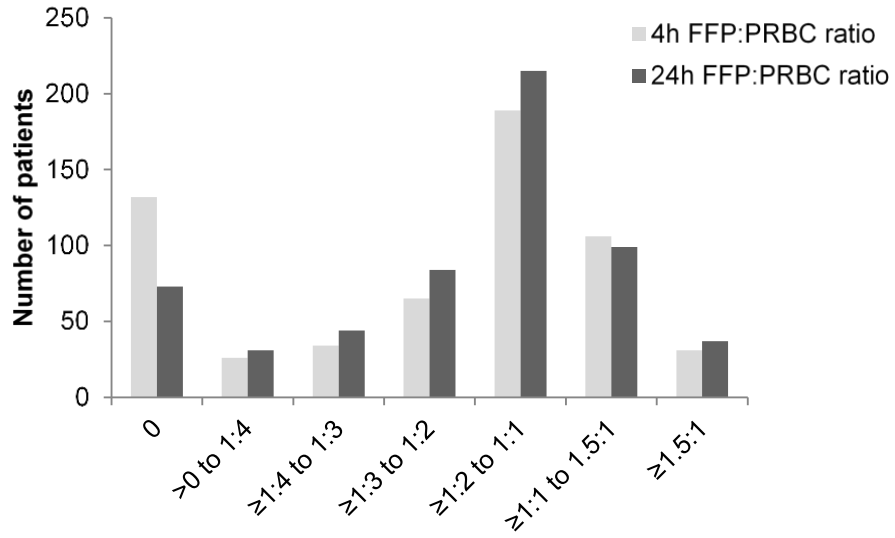
^aModels adjusted for age, injury mechanism, hypotension, abnormal heart rate, Glasgow coma scale, injury severity score, need for mechanical ventilation, and transfer status.

^bThere were no transfusion reactions.

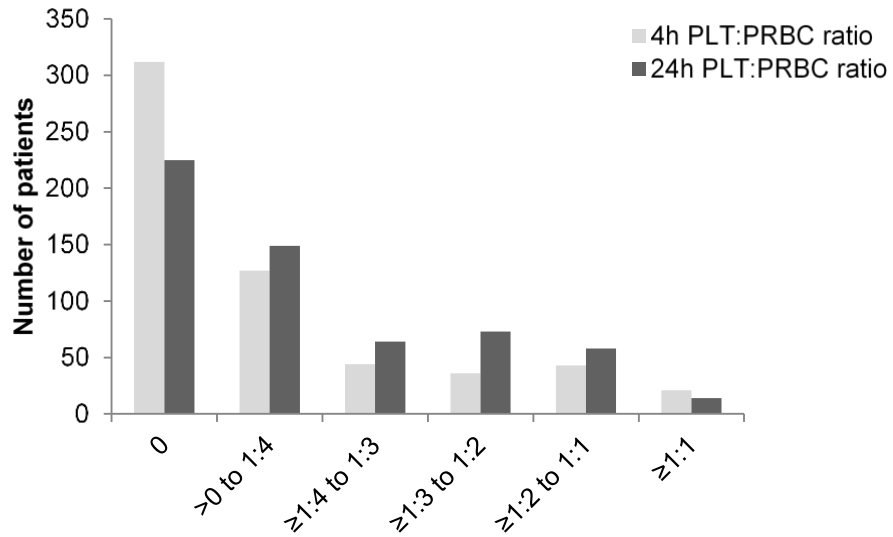
^cIncludes long term care facility, skilled nursing facility, intermediate care facility, or psychiatric hospital.

Supplemental Figure 1. Distribution of blood component ratios. (A.) Distribution of fresh frozen plasma to packed red blood cell (FFP:PRBC) ratio at 4 and 24 hours. (B.) Distribution of platelet to packed red blood cell (PLT:PRBC) ratio at 4 and 24 hours.

A.



B.



Supplemental Table 1. Outcomes and complications of 583 pediatric trauma patients receiving massive transfusion.

Characteristic	All (n=583)	FFP:PRBC			Platelet:PRBC		
		Low <1:2 (n=232)	Med ≥1:2 & <1:1 (n=215)	High ≥1:1 (n=136)	None 0 (n=225)	Low >0 & <1:2 (n=286)	High ≥1:2 (n=72)
Mortality							
24h mortality, No. (%)	115 (19.7)	55 (23.7)	44 (20.5)	16 (11.8)	32 (14.2)	70 (24.5)	13 (18.1)
In hospital mortality, No. (%)	247 (42.4)	104 (44.8)	97 (45.1)	46 (33.8)	80 (35.6)	132 (46.2)	35 (48.6)
Time to death, median (IQR), h	28 (6 to 56)	19 (5 to 50)	31 (8 to 62)	40 (18 to 66)	35 (7 to 66)	22 (6 to 50)	29 (12 to 43)
Complications, No. (%)							
Any	93 (15.6)	28 (12.1)	39 (18.1)	26 (19.1)	29 (12.9)	53 (18.5)	11 (15.3)
Deep vein thrombosis	25 (4.3)	6 (2.6)	10 (4.7)	9 (6.6)	8 (3.4)	17 (5.9)	0 (0)
Pneumonia	20 (3.4)	5 (2.2)	10 (4.7)	5 (3.7)	10 (4.4)	8 (2.8)	2 (2.8)
Unplanned return to operating room	16 (2.7)	5 (2.2)	6 (2.8)	5 (3.7)	4 (1.8)	9 (3.2)	3 (4.2)
Acute respiratory distress syndrome	13 (2.2)	4 (1.7)	7 (3.3)	2 (1.5)	4 (1.8)	8 (2.8)	1 (1.4)
Unplanned ICU admission or return to ICU	11 (1.9)	2 (0.9)	5 (2.3)	4 (2.9)	5 (2.2)	6 (2.1)	0 (0)
Acute kidney injury	11 (1.9)	2 (0.9)	6 (2.8)	3 (2.2)	1 (0.4)	7 (2.5)	3 (4.2)
Unplanned intubation	9 (1.5)	5 (2.2)	3 (1.4)	1 (0.7)	4 (1.8)	4 (1.4)	1 (1.4)
Stroke	8 (1.4)	1 (0.4)	4 (1.9)	3 (2.2)	1 (0.4)	6 (2.1)	1 (1.4)
Severe sepsis	5 (0.9)	2 (0.9)	2 (0.9)	1 (0.7)	1 (0.4)	3 (1.1)	1 (1.4)
Extremity compartment syndrome	4 (0.7)	0 (0)	2 (0.9)	2 (1.5)	1 (0.4)	2 (0.7)	1 (1.4)
Pulmonary embolism	3 (0.5)	1 (0.4)	2 (0.9)	0 (0)	0 (0)	3 (1.1)	0 (0)
Transfusion reaction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Supplemental Table 1. (Continued)

Characteristic	All (n=583)	FFP:PRBC			Platelet:PRBC		
		Low <1:2 (n=232)	Med ≥1:2 & <1:1 (n=215)	High ≥1:1 (n=136)	None 0 (n=225)	Low >0 & <1:2 (n=286)	High ≥1:2 (n=72)
Outcomes of survivors							
Hospital length of stay, median (IQR), d	20 (12 to 30)	19 (12 to 29)	20 (11 to 32)	22 (13 to 31)	17 (9 to 27)	23 (14 to 36)	24 (13 to 36)
ICU length of stay, median (IQR), d	12 (6 to 19)	12 (6 to 18)	10 (5 to 20)	13 (7 to 18)	10 (5 to 17)	13 (7 to 21)	11 (6 to 17)
Ventilator days, median (IQR), d	8 (3 to 13)	8 (3 to 13)	7 (3 to 14)	8 (4 to 13)	7 (2 to 12)	9 (3 to 14)	7 (3 to 13)
Disposition, No. (%)							
Home with or without services	170 (50.6)	64 (50.0)	61 (51.7)	45 (50.0)	76 (52.4)	71 (46.1)	23 (62.2)
Inpatient rehabilitation	147 (43.8)	55 (43.0)	52 (44.1)	40 (44.4)	61 (42.1)	74 (48.1)	12 (32.4)
Other care facility ^a	19 (5.7)	9 (7.0)	5 (4.2)	5 (5.6)	8 (5.5)	9 (5.8)	2 (5.4)

Abbreviations: FFP, fresh frozen plasma; PRBC, packed red blood cells; PLT, platelets; IQR, interquartile range; ICU, intensive care unit

^aIncludes long term care facility, skilled nursing facility, intermediate care facility, or psychiatric hospital