Fresh frozen plasma-first approach is independently associated with improved survival in severely injured patients undergoing massive transfusion

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BACKGROUND: Despite evidence supporting high fresh frozen plasma (FFP)–to–packed red blood cell (PRBC) ratios, the optimal initial blood product in severe injury is unknown. We hypothesized that an FFP-first approach is associated with improved survival.

METHODS: An observational Trauma Quality Improvement Program (2013–2021), including patients who received at least 5 units of PRBCs and 1 unit of FFP within four hours of arrival, was performed. Nonsurvivable injury patterns and pre-existing coagulopathy were excluded. Treatment effects were estimated with propensity score-weighted risk adjustment models, clustering by center. The primary outcome was six-hour mortality. Secondary outcomes were 24-hour and in-hospital mortality. A subanalysis was performed on the severe head-injured, and a sensitivity analysis examined inclusion criteria and additional blood products (platelets and cryoprecipitate). Effect modification was assessed for injury type.

RESULTS: A total of 50,580 patients were included, with 13,818 in the FFP-first approach. Mean age was 39 years, with 77% males, 60% blunt trauma, and a mean Injury Severity Score of 27. Subanalysis included 15,912 patients, and the exposure sensitivity analysis included 27,217 patients. Unadjusted six-hour, 24-hour, and in-hospital mortality for the PRBC-first approach were 9.8%, 15%, and 28%, respectively, compared with 8.9%, 14%, and 27% for the FFP-first approach. A PRBC approach was independently associated with worse six-hour (adjusted Odds Ratio [aOR], 1.10; 95% CI, 1.02–1.18), 24-hour (1.11; 1.05–1.18), and in-hospital mortality (1.06; 1.01–1.11). The subgroup analysis of the PRBC aOR was 1.08 (95% CI, 0.95–1.23). In the exposure sensitivity analysis, the PRBC aOR was 1.02 (95% CI, 0.94–1.09). The blood products analysis was congruent with the main analysis. Effect modification was not present for injury type; however, penetrating mechanism was significantly associated with early death.

CONCLUSIONS: Although the effect was modest in magnitude, a FFP-first approach was independently associated with improved survival through hospital discharge. Future prospective or randomized trials are warranted. (*J Trauma Acute Care Surg* 2026;00:000–000.

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KEY WORDS: Coagulopathy, hemorrhagic, massive transfusion, shock, resuscitation.

Hemorrhage accounts for 40% of trauma-related deaths and is the leading cause of preventable mortality.[1,2] Approximately one quarter of patients are coagulopathic upon arrival to the emergency department (ED) before aggressive resuscitation interventions.[3] Fresh frozen plasma (FFP) contains factors V, VIII, proteins C and S, and serves to replenish coagulation factors in a bleeding patient.[4]

Damage control resuscitation (DCR) is a strategy focused on effectively replenishing the blood loss of exsanguinating patients by using a balanced approach that includes red blood cells, plasma, platelets, and clotting factors. The currently recommended optimal transfusion ratio is 1:1:1 for platelets, FFP, and packed red blood cells (PRBCs).[5,6] Despite the demonstrated benefits of this approach, global acceptance and adherence to DCR principles are low. A survey conducted among United States trauma centers participating in the Trauma Quality Improvement Program (TQIP) revealed that up to 16% of these centers still utilize a resuscitation strategy that prioritizes PRBCs over plasma or platelets.[7]

While adherence to DCR protocols, including adherence to protocolized ratios, has been associated with improved outcomes,[8–13] the optimal order of blood

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product administration remains unknown. As a prior simulation study has demonstrated that the dilution of clotting factors within existing protocols remains underestimated,[14] we hypothesized that a FFP-first approach was associated with improved survival.

METHODS

Our institutional review board deemed this study exempt. This retrospective observational study complies with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (Supplemental Digital Content, Checklist, http://links.lww.com/TA/F493). The American College of Surgeons (ACS) is not responsible for any claims arising from works based on the original data, text, tables, or figures.

Study Design and Setting

We extracted data from the TQIP registry from 2013 to 2021.[15] This registry, part of the National Trauma Databank maintained by the ACS Committee on Trauma, includes over 900 voluntarily participating trauma centers. TQIP provides risk-adjusted data that enables trauma centers to benchmark their outcomes for severely injured patients. The TQIP data set focuses on individuals aged 16 to 89 who have suffered severe injuries, signified by an Abbreviated Injury Scale (AIS) score of 3 or higher.

Study Participants

This study included patients who received a massive transfusion, defined as at least five units of PRBCs[16,17] and one unit of FFP within four hours of their presentation to the ED.[18] Exclusions were made for: (1) patients with a nonsurvivable injury pattern (maximum AIS score of 6 in any body region); (2) patients who died within 30 minutes of arriving at the ED; (3) those with a history of cirrhosis, using anticoagulants, had a bleeding disorder, or had an advanced directive limiting care; (4) patients who were transferred; (5) patients aged 15 or younger or 90 or older; (6) patients who received more than 100 units of PRBCs, FFP, platelets, or cryoprecipitate within four hours of ED arrival due to potential inaccuracies in the data[18,19]; and (7) patients with missing exposure or outcome or facility key data.

Exposures

To classify patients into PRBC-first or FFP-first, we utilized the International Classification of Diseases (ICD) codes within the procedures files (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/TA/F493). By utilizing the procedure codes, we tabulated when the patients received PRBC and FFP, and classified patients into PRBC-first or FFP-first based on the first unit that was documented as being transfused first. If a PRBC and FFP were recorded at the same time, then this was excluded from the analysis.

Outcomes

The primary outcome was six-hour all-cause mortality, and secondary outcomes included 24-hour all-cause mortality and in-hospital all-cause mortality. In addition, a priori in-hospital adverse events related to clotting, infection, volume, cardiac arrest, unplanned events, total hospital length of stay, total intensive care unit length of stay, and total ventilator days were assessed.

Analytical Variables and Definitions

We extracted patient baseline demographics from TQIP, including: age, sex, race/ethnicity, primary payment method, patient pre-existing comorbidities (alcoholism, cerebrovascular accident, chemotherapy, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, diabetes mellitus, disseminated cancer, functionally dependent health status, hypertension, myocardial infarction, smoker, steroid use). In addition, we extracted the following injury demographics: heart rate, pulse oximetry, respiratory rate, systolic blood pressure, Glasgow Coma Scale (GCS) eyes, GCS motor, GCS verbal, injury severity score (ISS), maximum AIS by body region, and trauma mechanism. We extracted several hospital demographics, including ACS verification level, adult TQIP site, bed size, facility key (de-identified hospital identifier), hospital type, teaching status, and TQIP site.

We made the following variable changes: (1) Patients with multiple vital signs were collapsed down to one patient entry by selecting the first ED measurement. (2) We derived body mass index from height and weight and set those with a body mass index ≥ 188 to missing.[20] (3a) We extracted trauma type and trauma mechanism; however, they were found to be too multicollinear. As such, the trauma mechanism was used for the main analysis, while the trauma type was used to test for effect modification. (3b) For trauma type, ICD-9 and ICD-10 were collapsed to mitigate missingness. (3c) For trauma mechanism, the ICD-10 iteration had the least amount of missingness; as such, we used the ICD-10 iteration. (4) AIS and ISS required mapping, whose process has been described by the Association for the Advancement of Automotive Medicine. We ultimately used AIS 1998 as this had fewer missing values throughout the entire data set; however, ISS could only be mapped through AIS 2005.[21] (5) Lastly, we extracted platelets and cryoprecipitate and converted them to milliliters.

Statistical Analysis

A summary of the percentage of missingness is provided (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/TA/F493). Missing values were imputed using multiple imputation by chained equations under the assumption that the data were missing at random, and results from multiple imputed data sets are pooled using Rubin rule.[22] We assessed multicollinearity and identified the following issues: (1) Race and ethnicity, leading to the collapse of this

variable.[23] (2) Trauma type and mechanism; consequently, trauma mechanism was included in the propensity score model, whereas trauma type was excluded.

We calculated the probability of experiencing the exposures using a multivariable regression model (propensity score) to address imbalances in covariates across treatment groups. Subsequently, logistic regression models were pooled over the imputed data sets to estimate the inverse probability of treatment weights. We evaluated the covariate balance after the inverse probability of treatment weighting by comparing the estimated standardized mean differences with the commonly used threshold of 0.1.[24]

In our outcome models, we estimated the average treatment effect using a logistic generalized estimating equation model weighted by the inverse probability of treatment to control for potential confounders. This generalized estimating equation model extends the traditional weighted logistic regression to address center-level correlation. To account for this correlation, we used an independent working correlation matrix to compute robust sandwich estimates of standard errors. We evaluated potential effect modification-based types of injuries (blunt vs. penetrating) across the entire cohort and conducted a stratified analysis when effect modification was detected.

To further test the stability of our results, we conducted a series of sensitivity and subgroup analyses. First, to evaluate the impact of early mortality exclusion, we repeated the analysis, including patients who died within 30 minutes of arrival. Second, to focus on clinically meaningful differences in transfusion timing, we repeated the analysis after excluding patients with less than a 10-minute difference between PRBC and FFP administration. Third, we modified the inclusion criteria—which originally required receipt of five units of PRBCs and one unit of FFP—by instead requiring five units of FFP, more closely approximating a massive transfusion cooler.

Because additional blood products (including platelets and cryoprecipitate) may have been administered after exposure assignment and were not included in the primary analysis, we conducted additional sensitivity analyses that sequentially incorporated each product individually and then jointly to assess the robustness of the primary findings; these variables were also evaluated for effect modification. Finally, we performed a prespecified sub-analysis among patients with severe head injury (AIS Head ≥ 3).

Patient groups were evaluated through descriptive statistics. A two-sided p value of < 0.05 was considered statistically significant. All analyses were performed using R version 4.5.0 (R Foundation for Statistical Computing).

For the power analysis, we used a logistic regression model, which is appropriate for binary outcomes and allows for the estimation of odds ratios (ORs). Based on a total sample size of 50,580 subjects, the study is estimated to have at least 80% power at a two-sided significance level of 0.05 to detect small effect sizes. Specifically, this corresponds to ORs > 1.08 or < 0.92, indicating the minimum effect sizes that the study is likely to detect reliably. Accordingly, the study is expected to have sufficient statistical power to identify clinically meaningful associations unless the true effect size is smaller than these thresholds.

RESULTS

Characteristics of Study Population

A total of 50,580 patients were eligible for the analysis (36,762 PRBC first approach, 13,818 FFP first approach; Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/TA/F493). The mean age was 39 (17). 77% (38,948/50,580) were males. About 60% (29,980/50,580) had a blunt injury mechanism. Mean ISS was 27 (13). The percentage of missingness before multiple imputation is included. The baseline patient and hospital characteristics of the included patient population by exposure status before multiple imputation are included in an abridged form (Table 1) and an expanded

TABLE 1. Unadjusted Baseline Characteristics

Covariate	FFP (N = 13,818)	PRBC (N = 36,762)	SMD	*p*
Age (y)	39 (17)	39 (18)	0.02	0.05
Sex (male), n (%)	10,739 (78)	28,209 (77)	0.03	< 0.01
Body mass index (kg/m^2)	28 (10)	29 (11)	0.05	0.001
Trauma type, n (%)			0.04	< 0.001
Blunt	8,012 (58)	21,968 (60)	—	—
Penetrating	5,690 (42)	14,402 (40)	—	—
Injury severity score	26 (13)	27 (13)	0.05	< 0.001
Heart rate	106 (32)	107 (32)	0.05	< 0.001
Pulse oximeter	95 (12)	94 (12)	0.01	0.8
Respiratory rate	21 (8)	21 (8)	0.01	0.2
Systolic blood pressure	106 (36)	105 (35)	0.03	< 0.001
Glasgow Coma Scale Eye, n (%)			0.03	0.05
1	4,638 (34)	12,373 (34)	—	—
2	482 (3.6)	1,432 (4.0)	—	—
3	1,091 (8.0)	2,724 (7.6)	—	—
4	7,344 (54)	19,397 (54)	—	—
Glasgow Coma Scale Motor, n (%)			0.03	0.04
1	4,155 (31)	11,055 (31)	—	—
2	142 (1.0)	412 (1.1)	—	—
3	159 (1.2)	513 (1.4)	—	—
4	667 (4.9)	1,890 (5.3)	—	—
5	1,010 (7.5)	2,805 (7.8)	—	—
6	7,414 (55)	19,244 (54)	—	—
Glasgow Coma Scale Verbal, n (%)			0.03	0.06
1	4,737 (35)	12,666 (35)	—	—
2	656 (4.8)	1,912 (5.3)	—	—
3	334 (2.5)	956 (2.7)	—	—
4	1,940 (14)	5,202 (14)	—	—
5	5,882 (43)	15,188 (42)	—	—
4-h cryoprecipitate	36 (124)	37 (125)	0.01	0.11
4-h platelets	218 (371)	241 (379)	0.06	< 0.001

SMD, standardized mean difference.

form (Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/TA/F493). At baseline, the patients' characteristics between exposure arms were mostly balanced; however, a couple of the covariates' mean standardized differences were >0.1, such as mechanism of injury, trauma center bed size, trauma center teaching status, and ACS verification level. Distributions of time to first transfused unit (PRBCs in the PRBC-first cohort and FFP in the FFP-first cohort) are, in addition, depicted using violin plots.

Propensity Score Weighting

Propensity score weighting achieved balance across all covariates (mean standardized differences < 0.1), as shown in the abbreviated version in Table 2 and in more detail in the Supplemental Digital Content (Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/TA/F493). In addition, histograms displaying the propensity score by exposure status to assess overlap and positivity violations, along with the mean standardized differences, can be found in the Supplemental Digital Content (Supplemental Figs. 2 and 3, Supplemental Digital Content 1, http://links.lww.com/TA/F493).

TABLE 2. Propensity Score-Weighted Baseline Characteristics

Covariate	FFP (N = 50,793)	PRBC (N = 50,536)	SMD	*P*
Age (y)	39 (17)	39 (18)	0.00	>0.9
Sex (male), n (%)	39,199 (50)	39,033 (50)	0.00	0.9
Body mass index (kg/m^2)	29 (11)	29 (11)	0.00	0.6
Injury severity score	27 (14)	27 (13)	0.00	>0.9
Heart rate	107 (32)	107 (32)	0.00	0.6
Pulse oximeter	94 (12)	94 (12)	0.01	0.15
Respiratory rate	21 (8)	21 (8)	0.01	>0.9
Systolic blood pressure	105 (36)	105 (35)	0.01	>0.9
Glasgow Coma Scale Eye, n (%)			0.01	>0.9
1	17,643 (50)	17,425 (50)	—	—
2	1,995 (50)	1,957 (50)	—	—
3	3,877 (50)	3,876 (50)	—	—
4	27,278 (50)	27,278 (50)	—	—
Glasgow Coma Scale Motor, n (%)			0.01	>0.9
1	15,747 (50)	15,565 (50)	—	—
2	594 (51)	570 (49)	—	—
3	701 (50)	688 (50)	—	—
4	2,602 (50)	2,610 (50)	—	—
5	3,816 (50)	3,889 (50)	—	—
6	27,333 (50)	27,215 (50)	—	—
Glasgow Coma Scale Verbal, n (%)			0.01	>0.9
1	18,076 (50)	17,834 (50)	—	—
2	2,632 (50)	2,621 (50)	—	—
3	1,282 (50)	1,300 (50)	—	—
4	7,240 (50)	7,276 (50)	—	—
5	21,563 (50)	21,505 (50)	—	—

SMD, standardized mean difference.

Unadjusted Outcomes

The overall six-hour mortality rates before inverse probability treatment weighting were 3,614 (9.8%) PRBC and 1,235 (8.9%) FFP (p <0.001). While 24-hour mortality was 5,631 (15%) PRBC and 1,918 (14%) FFP (p < 0.001), and in-hospital mortality was 10,210 (28%) PRBC and 3,679 (27%) FFP (p = 0.01; Table 3).

Adjusted Outcomes

For the main analysis, a total weighted sample size of 101,329 patients was included, 50,536 in the PRBC-first approach cohort and 50,793 in the FFP-first approach cohort. When comparing PRBC-first approach versus FFP-first approach, PRBC-first approach was independently associated with worse survival at hours six (OR, 1.10, 95% CI, 1.02–1.18, p = 0.02), hour 24 (OR, 1.11, 95% CI, 1.05–1.18, p < 0.001) and at discharge (OR, 1.06, 95% CI, 1.01–1.11, p = 0.03; Table 3, Fig. 1).

Adverse Events and Length of Stay Outcomes

The PRBC-first approach had more cardiac arrest and catheter-associated urinary tract infections (p < 0.05) on adjusted analysis. There was no statistically significant difference in intensive care unit stay, hospital length of stay, and mechanical ventilator days (Table 4).

Effect Modification Analysis

There was no significant evidence of effect modification by injury type for the effect of the PRBC-first approach on mortality. However, penetrating trauma was significantly associated with worse survival at six hours (OR, 1.23; 95% CI, 1.08–1.41; p < 0.01) but not at 24 hours (OR, 0.97; 95% CI, 0.87–1.08; p = 0.59). By hospital discharge, it was significantly associated with a mortality benefit (OR, 0.63; 95% CI, 0.58–0.68; p < 0.0001; Table 5).

TABLE 3. Mortality Outcomes

Outcome	PRBC	FFP*	*p*
6-h mortality			
Unadjusted, n (%)	3,614 (9.8)	1,235 (8.9)	<0.01
Adjusted OR (95% CI)	1.10 (1.02–1.18)		0.02
Absolute risk difference	0.01 (0.002–0.01)		0.02
24-h mortality			
Unadjusted, n (%)	5,631 (15)	1,918 (14)	<0.001
Adjusted OR (95% CI)	1.11 (1.05–1.18)		<0.001
Absolute risk difference	0.01 (0.006–0.02)		<0.001
In-hospital mortality			
Unadjusted, n (%)	10,210 (28)	3,679 (27)	0.01
Adjusted OR (95% CI)	1.06 (1.01–1.11)		0.03
Absolute risk difference	0.01 (0.001–0.02)		0.03

*The FFP first approach cohort is the reference group for the p-value comparisons

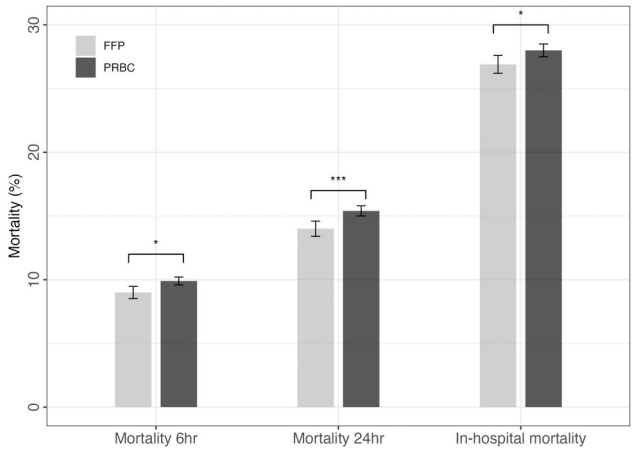

FIGURE 1. Margins of mortality (adjusted predicted probability of mortality) with 95% CIs of PRBC first approach and FFP first approach.

Survival Bias Sensitivity Analysis (Inclusion of Death Within 30 Minutes)

In the sensitivity analysis that incorporated patients who died within 30 minutes of arrival, the overall weighted sample size was 113,610, including 56,735 patients in the PRBC-first cohort and 56,876 in the FFP-first cohort. In this analysis, a PRBC-first approach was associated with worse survival. While this association did not reach statistical significance at six hours (OR, 1.05, 95% CI, 0.99–1.11; $p = 0.13$), it was statistically significant at 24 hours (OR, 1.06, 95% CI, 1.02–1.12; $p < 0.01$) and at hospital discharge (OR, 1.05, 95% CI, 1.01–1.10; $p = 0.02$).

TABLE 4. Adjusted Length of Stay and Adjusted Adverse Events.

Outcome	PRBC,* OR (95% CI; *p*)
Length of stay	
Total intensive care unit days	1.24 (0.96–1.60; 0.10)
Total length of stay days	1.04 (0.55–1.59; 0.83)
Total ventilator days	1.18 (0.96–1.45; 0.12)
Adverse events	
Acute kidney injury	1.00 (0.01–1.11; 0.96)
Acute myocardial infarction	0.89 (0.64–1.23; 0.48)
Acute respiratory distress syndrome	0.97 (0.83–1.13; 0.70)
Cardiac arrest	1.11 (1.02–1.19; <0.01)
Catheter-associated urinary tract infection	1.31 (1.04–1.67; 0.02)
Central line-associated blood infection	1.10 (0.77–1.58; 0.59)
Cerebrovascular accident	0.99 (0.93–1.19; 0.92)
Deep vein thrombosis	1.00 (0.91–1.10; 0.93)
Organ space surgical infection	1.07 (0.90–1.28; 0.42)
Pulmonary embolism	0.97 (0.85–1.12; 0.70)
Sepsis	1.04 (0.90–1.22; 0.59)
Unplanned intensive care unit admission	0.98 (0.87–1.09;0.68)
Unplanned intubation	1.07 (0.95–1.20; 0.28)
Unplanned return to the operating room	1.04 (0.95–1.13; 0.41)
Ventilator-associated pneumonia	0.94 (0.84–1.06; 0.32)

*The Fresh Frozen Plasma first approach cohort is the reference group for the p-value comparisons

Excluding Patients With Less Than a 10-Minute Difference Between Packed Red Blood Cell and Fresh Frozen Plasma Administration Sensitivity Analysis

In the sensitivity analysis excluding patients with a difference of <10 minutes between PRBC and FFP administration, the overall weighted sample size was 57,700 patients, with 28,715 in each exposure cohort. Consistent with the primary analysis, a PRBC-first approach was associated with worse survival at six hours (OR, 1.22, 95% CI, 1.07–1.39; $p < 0.01$), 24 hours (OR, 1.21, 95% CI, 1.09–1.34; $p < 0.001$), and at hospital discharge (OR, 1.07, 95% CI, 0.99–1.16; $p = 0.08$). However, it did not reach statistical significance at hospital discharge, which may be related to our reduced sample size.

Exposure Sensitivity Analysis Requiring 5 Units of Fresh Frozen Plasma

For the sensitivity analysis on the exposure definition, the overall weighted sample size was 54,514 patients, with 27,207 in the PRBC-first approach cohort and 27,307 in the FFP-first approach cohort. A PRBC-first approach was associated with worse survival; however, it was not statistically significant at hours six (OR, 1.02; 95% CI, 0.94–1.11; $p = 0.62$) or hours 24 (OR, 1.05; 95% CI, 0.97–1.13; $p = 0.21$).

Blood Product Sensitivity Analysis

The blood product sensitivity analysis was congruent with our main analysis (Table 5). The unadjusted violin plots by exposure status for four-hour transfusion volumes of PRBC, FFP, platelets, and cryoprecipitate are included (Supplemental Figs. 4–7, Supplemental Digital Content 1, http://links.lww.com/TA/F493).

Head Injured Subgroup Analysis

Among patients with a head injury, the total weighted sample size comprised 31,865 patients, with 15,903 in the PRBC-first approach cohort and 15,962 in the FFP-first approach cohort. A PRBC-first approach was associated with worse survival; however, it was not statistically significant at hours six (OR, 1.08, 95% CI, 0.95–1.23, $p = 0.25$) or hours 24 (OR, 1.06; 95% CI, 0.96–1.16; $p = 0.26$).

DISCUSSION

In this large nationwide analysis of severely injured patients undergoing massive transfusion, we found that a FFP-first approach was independently associated with improved survival through hospital discharge. In a sen-

TABLE 5. Exploratory Blood Product Analysis and Penetrating Mechanism Analysis

	OR (95% CI; *p*)		OR (95% CI; *p*)
6-h mortality, main analysis		In-hospital mortality, main analysis	
PRBC-first approach	1.10 (1.02–1.18; 0.02)	PRBC-first approach	1.06 (1.01–1.11; 0.03)
6-h mortality, penetrating adjusted		In hospital mortality, penetrating adjusted	–
PRBC-first approach	1.09 (0.98–1.21; 0.11)	PRBC-first approach	1.04 (0.98–1.11; 0.16)
Penetrating	1.23 (1.08–1.41; 0.003)	Penetrating	0.63 (0.58–0.68; < 0.0001)
PRBC*penetrating	1.02 (0.88–1.19; 0.77)	PRBC*penetrating	1.03 (0.93–1.13; 0.59)
6-h mortality, cryoprecipitate adjusted		In-hospital mortality, cryoprecipitate adjusted	
PRBC-first approach	1.12 (1.03–1.21; < 0.01)	PRBC-first approach	1.07 (1.01-1.13; 0.02)
Cryoprecipitate	1.001 (1.001–1.002; < 0.0001)	Cryoprecipitate	1.002 (1.002–1.003; < 0.0001)
PRBC*cryoprecipitate	1 (1–1; 0.241)	PRBC*cryoprecipitate	1 (1–1; 0.88; < 0.0001)
6-h mortality, platelets adjusted		In-hospital mortality, platelets cryoprecipitate adjusted	–
PRBC-first approach	1.17 (1.06–1.28; 0.001)	PRBC-first approach	1.10 (1.03–1.18; 0.004)
Platelets	1.001 (0.95, 1.06; 0.97)	Platelets	1.001 (1.001–1.001; < 0.0001)
PRBC*platelets	1 (1–1; 0.08)	PRBC*platelets	1 (1–1; 0.092)
6-h mortality, adjusted for all		In-hospital mortality, adjusted for all	
PRBC-first approach	1.10 (1.02–1.19; 0.012)	PRBC-first approach	1.06 (1.01-1.12; 0.02)
Cryoprecipitate	1 (1–1; < 0.0001)	Cryoprecipitate	1.001(1.001–1.001; < 0.0001)
Platelets	1.001 (1.001–1.001; < 0.0001)	Platelets	1.001(1.001–1.001; < 0.0001)
Penetrating	1.20 (1.11–1.30; < 0.0001)	Penetrating	0.59 (0.56–0.62; < 0.0001)
24-h mortality, main analysis			
PRBC-first approach	1.11 (1.05–1.18; < 0.001)		
24-h mortality, penetrating adjusted			
PRBC-first approach	1.06 (0.78–1.15; 0.16)		
Penetrating	0.97 (0.87–1.08; 0.59)		
PRBC*penetrating	1.13 (0.995–1.28; 0.059)		
24-h mortality, cryoprecipitate adjusted			
PRBC-first approach	1.11 (1.04–1.19; 0.002)		
Cryoprecipitate	1.002 (1.001–1.002; < 0.0001)		
PRBC*cryoprecipitate	1 (1–1; 0.54)		
24-h mortality, platelets adjusted			
PRBC-first approach	1.16 (1.07-1.25; < 0.001)		
platelets	1.001 (1.001-1.001; < 0.0001)		
PRBC*platelets	1 (1-1; 0.28)		
24-h mortality, platelets adjusted			
PRBC-first approach	1.12 (1.05–1.19; < 0.001)		
Cryoprecipitate	1.001 (1–1.001; < 0.0001)		
Platelets	1.001 (1.001–1.001; < 0.0001)		
Penetrating	0.99 (0.92–1.05; 0.64)		

sitivity analysis adjusting for other blood products, our findings remained true. While head injury was not associated with a difference in the effect of the FFP-first approach versus the PRBC-first approach on mortality, we found that the penetrating patient population was significantly associated with worse early survival.

Previous research has shown that plasma-based resuscitation is superior; however, the comparator was normal saline, making generalizations to balanced ratio resuscitation difficult. The rationale for FFP superiority is based on normal saline's tendency to worsen tissue plasminogen activator-mediated fibrinolysis, while FFP does not have this effect.[25,26] This difference is partly attributed to FFP containing high concentrations of protease inhibitors, which help regulate fibrinolysis, as well as fibrinogen and other factors that promote the formation of a clot resistant to fibrinolysis.[27] The difference in mortality favoring an FFP-first approach may stem from

PRBCs lacking enrichment from these same proteins. Another plausible mechanism includes the attenuation of an inflammatory or endothelial response, as noted in the Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock study, which reported a mortality benefit that occurred early, within the first few hours, and persisted through 30 days.[28] Notably, patients in the plasma group did not have a higher incidence of inflammation-mediated complications, such as multiorgan failure, acute lung injury-acute respiratory distress syndrome, or nosocomial infections, supporting the inflammatory mediating effects of FFP.[29,30]

The penetrating trauma population being associated with worse early survival is not surprising, as it has been previously described in the literature.[31,32] Prior works have demonstrated a different coagulation phenotype in penetrating trauma patients, making this patient population more susceptible to coagulopathic bleeding.[33] By the time of hospital discharge, a penetrating mechanism had a mortality benefit as the blunt patient population likely succumbed to other injuries, such as head injuries. This is confirmed with our data, as the maximum AIS of the head and IQR was 2 (0,4) for blunt versus 0 (0,0) for penetrating. Furthermore, at discharge, more than 50% of the deaths had a maximum AIS of the head of ≥ 3 as compared with only a third of the deaths that occurred at hour six. While we noticed statistically significant differences in mortality for the penetrating patient population, we did not notice a difference in effect for the FFP-first approach versus the PRBC-first approach on mortality (effect modification). It is plausible that we may have reached statistical significance had we included more patients, which would have resulted in a narrower CI around the point estimate.

The brain-injured patient population remains a subset where plasma may be beneficial,[34–36] as traumatic brain injury is prone to acute coagulation disorders due to the local release of tissue factors and platelet dysfunction.[37,38] Early administration of FFP has been shown to reduce the size of brain lesions and associated swelling when compared with normal saline, six hours post injury.[35] In addition, it diminishes the degree of neurological impairment, enhances the rate of recovery, and preserves cognitive function.[34] This positive effect is believed to stem from FFP's ability to reverse endotheliopathy, restore tight junctions at the glycocalyx level, and inhibit inflammation. Currently, the FFP in Traumatic BRAin Injury (FIT-BRAIN) Trial is underway, which aims to investigate the effectiveness of FFP treatment in individuals with moderate to severe traumatic brain injury.[39] In our study, we performed a sub-analysis among the brain-injured patient population. With only 4,425 patients in the FFP-first cohort before IPTW, our results may not have been adequately powered to achieve statistical significance in a sub-analysis. However, a PRBC-first approach was associated with increased mortality.

It is important to acknowledge several limitations in our analysis. First, the procedure codes for the blood product transfusion have not been validated within TQIP, nor have they been validated in any other registry or electronic medical record databases. Secondly, a second cause of misclassification bias could be related to the timestamps of the procedure codes. Thirdly, there is the potential for survival bias. Many centers have PRBC available within the trauma bay or resuscitation areas, but FFP might be less readily available for point-of-care resuscitation. If a center does not have thawed plasma on hand, this may incur delays in FFP transfusion. To mitigate the risk of survival bias, we excluded patients who expired within 30 minutes. Fourth, although our results did not reach statistical significance in our sensitivity analysis on the exposure definition, the point estimate was congruent with the main analysis. This may be related to power, with only 6,443 patients in the FFP-first cohort before IPTW. This lack of significance could also be related to misclassification bias, where it becomes difficult to accurately record transfusion data timestamps when the volume reaches at least 10 units within four hours. Lastly, as a general trauma registry, detailed information about resuscitation adjuncts—such as tranexamic acid and vasopressin—administered fluid volume, laboratory tests like viscoelastic assays and lactic acid levels, hemostatic adjuncts, the age of blood products, and the cause of death is not available in TQIP.[40]

As a validated trauma registry, our results are relevant to trauma centers throughout North America. Furthermore, since whole blood data were incorporated into TQIP in the later years of the study, there was a significant amount of missing data. As a result, multiple imputation was not a feasible approach to address this missingness. Therefore, we are unable to generalize our findings to scenarios involving whole blood-based resuscitation or prehospital plasma-heavy systems.[41]

Currently, the existing scientific evidence on the FFP-first approach primarily compares FFP to normal saline in patients with head injuries or examines the specific ratio of FFP to PRBCs. However, there is a lack of data regarding which type of blood product should be administered first in exsanguinating patients. We believe that future prospective observational or randomized controlled trials should include precise transfusion timestamps in their statistical analysis plan. This would help assess the effects of an FFP-first versus a PRBC-first approach and build on previous DCR research aimed at reducing the time spent in trauma-induced coagulopathy.

CONCLUSION

A FFP-first approach, when compared with a PRBC-first approach, was independently associated with a reduction in mortality in severely injured patients undergoing massive transfusion. As most resuscitation protocols for exsanguinating patients prioritize a PRBC-first approach, future prospective and randomized clinical trials are needed to validate our findings and inform future clinical practice guidelines supporting a FFP-first approach.

AUTHORSHIP

A.M.H., R.D.C, and K.Y. participated in designing the study. A.M.H. participated in searching the literature. A.M.H., R.D.C, and K.Y. participated in collecting the data. A.M.H., R.D.C., and K.Y. participated in analyzing the data. A.M.H., R.J.W., T.J.T., K.A.B., J.H.L., and M.A.d.M. participated in data interpretation. A.M.H. participated in drafting the article, which all authors critically revised and approved.

DISCLOSURE

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