The Association of Blood Component Use Ratios With the Survival of Massively Transfused Trauma Patients With and Without Severe Brain Injury

Philip C. Spinella, MD, Charles E. Wade, PhD, Lorne H. Blackbourne, MD, Matthew A. Borgman, MD, Lee A. Zarzabal, MS, Fei Du, MS, Jeremy G. Perkins, MD, Marc Maegele, MD, Martin Schreiber, MD, John R. Hess, MD, Kenneth M. Jastrow, III, MD, Ernest A. Gonzalez, MD, John B. Holcomb, MD, Rosemary Kozar, MD, and the Trauma Outcomes Group

Background: The effect of blood component ratios on the survival of patients with traumatic brain injury (TBI) has not been studied.

Methods: A database of patients transfused in the first 24 hours after admission for injury from 22 Level I trauma centers over an 18-month period was queried to find patients who (1) met different definitions of massive transfusion (5 units red blood cell [RBC] in 6 hours vs. 10 units RBC in 24 hours), (2) received high or low ratios of platelets or plasma to RBC units ($<$1:2 vs. $\geq$1:2), and (3) had severe TBI (head abbreviated injury score $\geq$3) (TBI+).

Results: Of 2,312 total patients, 850 patients were transfused with $\geq$5 RBC units in 6 hours and 807 could be classified into TBI+ (n = 281) or TBI− (n = 526). Six hundred forty-three patients were transfused with $\geq$10 RBC units in 24 hours with 622 classified into TBI+ (n = 220) and TBI− (n = 402). For both high-risk populations, a high ratio of platelets:RBCs (not plasma) was independently associated with improved 30-day survival for patients with TBI+ and a high ratio of plasma:RBCs (not platelets) was independently associated with improved 30-day survival in TBI− patients.

Conclusions: High platelet ratio was associated with improved survival in TBI+ patients while a high plasma ratio was associated with improved survival in TBI− patients. Prospective studies of blood product ratios should include TBI in the analysis for determination of optimal use of ratios on outcome in injured patients.

Key Words: Transfusion, Mortality, Red Blood Cell, Plasma, Platelets.

(*J Trauma.* 2011;71: S343–S352)

Submitted for publication March 10, 2011.
Accepted for publication June 6, 2011.

From the Department of Pediatrics (P.C.S.), St. Louis Children's Hospital, St. Louis, Missouri; US Army Institute of Surgical Research (P.C.S., C.E.W., L.H.B.), San Antonio, Texas; Department of Pediatrics (M.A.B.), Children's Hospital, Boston, Massachusetts; Department of Epidemiology and Biostatistics (L.A.Z., F.D.), University of Texas health Science Center, San Antonio, Texas; Department of Medicine (J.G.P.), Walter Reed Army Medical Center, Washington, DC; Department of Surgery (M.M.), Merheim Medical Center, Cologne, Germany; Department of Surgery (M.S.), Oregon Health & Science University, Portland, Oregon; Department of Pathology (J.R.H.), R Adams Cowley Shock Trauma Center, Baltimore, Maryland; and Division of Acute Care Surgery (K.M.J., E.A.G., J.B.H., R.K.), Center for Translational Injury Research, University of Texas Health Science Center, Houston, Texas.

Address for reprints: Philip C. Spinella, MD, FCCM, Division of Critical Care Medicine, St. Louis Children's Hospital, 1 Children's Place/Campus box 8116, St. Louis, MO 63110; email: spinella_p@wustl.kids.edu.

DOI: 10.1097/TA.0b013e318227ef2d

A component of damage control resuscitation is hemostatic resuscitation which is the early use of red blood cells (RBCs), plasma, and platelets in a 1:1:1 unit ratio for patients with life-threatening bleeding secondary to trauma.[1–5] A potential benefit of hemostatic resuscitation is that increased early use of plasma and platelets will decrease death from hemorrhage by rapidly correcting the coagulopathy of trauma.[1–5] There may also be other potential benefits of hemostatic resuscitation on endothelial repair to include the blood brain barrier (BBB). A recent review of blood product ratio studies indicates that a high ($\geq$1:2) fresh frozen plasma (FFP):RBC ratio and high platelets (PLT):RBC ratio are associated with improved 30-day survival for patients receiving a massive transfusion.[2]

Although there are data to support the hypothesis that hemostatic resuscitation is associated with decreased death from hemorrhage in severely injured populations,[6–13] the effect of severe traumatic brain injury (TBI) in patients with multiple injures has not been studied. Severe trauma patients with and without severe TBI have been noted to have similar incidence of early coagulopathy (22–32%) on admission, which has also been associated with increased risk of death in both populations.[14–17] However, there are differences between patients with and without severe TBI that might lead to dissimilar results for studies evaluating outcomes related to the use of hemostatic resuscitation. Early coagulopathy for patients with severe TBI has been noted to resolve more quickly than coagulopathy in patients without severe TBI.[17] As expected, patients with severe TBI die predominantly secondary to brain injury and patients without severe TBI die predominantly from hemorrhage.[18–20] The importance of controlling intracranial bleeding on survival in patients with severe TBI may also differentiate this patient group compared with other severe trauma patients. As severe TBI can be fatal, due to primary neuronal injury from edema and cytotoxic injury or due to uncontrolled bleeding or both, it is unknown whether increased early transfusion of plasma and platelets will decrease death in this population. As a result of these differences between patients with and without severe TBI, it is plausible that increased ratios of plasma or platelets to RBCs may have differential effects on outcomes for a population at high risk of mortality.

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 AUG 2011	**N/A**	**-**

4. TITLE AND SUBTITLE

The association of blood component use ratios with the survival of massively transfused trauma patients with and without severe brain injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Brasel K. J., Vercruysse G., Spinella P. C., Wade C. E., Blackbourne L. H., Borgman M. A., Zarzabal L. A., Du F., Perkins J. G., Maegele M., Schreiber M., Hess J. R., Jastrow 3rd K. M., Gonzalez E. A., Holcomb J. B., Kozar R., Vercruysse G., MacLeod J., Dutton R. P., Duchesne J. C., McSwain N. E., Muskat P., Johannigamn J., Cryer H. M., Cryer H. M., Pittet J. F., Knudson P., De Moya M. A., Tieu B., Brundage S. I., Napolitano L. M., Brunsvold M., Sihler K. C., Beilman G., Peitzman A. B., Zenait M. S., Sperry J., Alarcon L., Croce M. A., Minei J. P., Stewart R. M., Cohn S. M., Mickalek J. E., Bulger E. M., Cotton B. A., Nunez T. C., Ivatury R., Meredith J. W., Miller P., Pomper G. J., Marin B.,

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**10**	

Major criticisms of previously published retrospective studies that have evaluated the association of transfusion ratios on outcomes in trauma patients include questions of survival bias and the implications of definitions of massive transfusion.[2,21] Survival bias is present when patients arrive, get several units of red blood cells (RBCs), die before the plasma gets thawed, and get counted as low ratio patients. Most recent publications have defined massive transfusion as ≥10 units of RBCs in the first 24 hours after admission.[2] However, mortality has been documented to increase significantly after 5 units have been transfused in the first day of admission,[22,23] and the majority of hemorrhagic deaths and blood resuscitation occur in the first 6 hours after admission.[20,24–26] As a result, alternative groups of patients at risk of hemorrhagic shock have been analyzed to include those transfused 8 units to 10 units of RBC within 3 hours to 12 hours from admission.[11,27–29] In this large retrospective registry study, our primary objective was to determine whether high ratios of either platelets or plasma were independently associated with improved 30-day survival for patients with and without severe TBI at high risk of mortality.

METHODS

Data for this study are from a retrospective multicenter Institutional Review Board-approved trial of transfused trauma patients who were transported from the scene of an event to 1 of 22 Level I trauma centers over an 18-month period (July 1, 2005, to December 15, 2006). Data integrity for this data set was verified by one research coordinator at the US Army Institute of Surgical Research, San Antonio, TX. Two separate inclusion criteria were used to define patient populations at high risk of death. The first was patients transfused ≥5 units of RBCs in the first 6 hours. The second was patients transfused ≥10 units of RBCs in the first 24 hours. Patients who died within the first hour of admission were excluded in the primary analysis. Severe TBI (TBI+) was defined as head abbreviated injury scale (AIS) score ≥3 and TBI− for patients with head AIS score <3. A high ratio was defined as ≥1:2. Apheresis platelet units were converted to pooled platelets for calculations of ratios (1 apheresis platelet unit = 6 pooled platelet units). Platelet (PLT:RBC) and plasma (FFP:RBC) ratios were calculated at 6 hours and 24 hours from admission. Thirty-day mortality was the primary outcome. Comparisons of all variables collected were made between high and low ratio groups for both platelets and plasma. This was performed for both TBI+ and TBI− groups. Cause of death was categorized as multiple organ failure (MOF), truncal hemorrhage, head injury, airway problems, or others and validated by the senior investigator at each site. Parametric data are described as mean (±standard deviation) and nonparametric data as median (interquartile range). The univariate association of each variable with 30-day mortality was modeled with Cox regression and determined by the corresponding hazard ratios.

Propensity scores were created for having received high or low ratio for both platelets and plasma using logistic regression models. Each model predicted the probability of having received a high or low ratio of platelets or plasma with adjustment for significant admission variables and the amount of cryoprecipitate given in the same amount of time as the defined massive transfusion group. Admission variables were chosen from univariate tests for a significant association ($p < 0.1$) with ratio group within each of the massively transfused cohorts. When admission international normalized ratio (INR) and pH were both significant, only INR was used due to high correlation between these two variables (data not shown). Admission temperature was excluded from the propensity score but included as a candidate covariate in the adjusted proportional hazards models. The logistic regression models were performed using backward selection with selection criteria of $p < 0.05$. All variables were tested for association with ratio group based on parametric tests for normally distributed data and nonparametric tests for skewed data. Normality assumptions were tested using Shapiro-Wilks test and visual examination of histograms. Unadjusted Kaplan-Meier curves were also constructed to compare survival for patient study groups with the log-rank test used to determine significance ($p < 0.05$). The final Cox regression models were performed on 30-day mortality on each massive transfusion group and separately for TBI+ and TBI− patients. Each model included the propensity scores for both platelet ratio and plasma ratio from the above-described logistic models and any significant variables ($p < 0.1$) from univariate Cox regression models on the same outcome. If a variable was significant in the univariate Cox Regression but was previously used for adjustment in the propensity model, it was not included in the multivariate Cox model. In the final multivariate Cox models, backward selection was used on all significant variables with selection criteria of $p < 0.05$; the propensity scores were always retained. All statistical testing was two-sided with a significance level of 5% and was performed with SAS version 9.2 for Windows (SAS Institute, Cary, NC). All graphical presentations were created using R version 2.9.0.

RESULTS

Of 2,312 patients receiving at least one transfusion in the Emergency Department (Fig. 1) who did not die within the first 60 minutes, there were 850 patients who were transfused ≥5 units of RBCs in the first 6 hours (≥5 RBC in 6 hours) and 643 patients transfused ≥10 units of RBCs in the first 24 hours (≥10 RBC in 24 hours). For the 850 patients in the ≥5 RBC in 6-hour group, there were 281

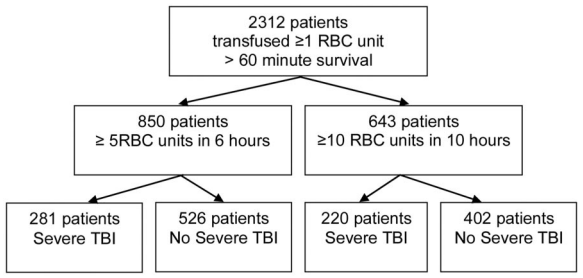


Figure 1. Distribution of patients in each cohort of patients studied.

TABLE 1. Demographics on Admission for TBI+ Patients Receiving High and Low Platelet (PLT:RBC) Ratios*

	≥5 Units RBC/6 h				≥10 Units RBC/24 h			
Variables	**N**	**High**	**Low**	***p***	**N**	**High**	**Low**	***p***
Age (yr)	281	40 (26–54)	37 (23–55)	0.53	220	38 (25–52)	38 (25–58)	0.48
Male, n (%)	281	66 (73.3)	121 (63.4)	0.1	220	74 (71.2)	69 (59.5)	0.07
Blunt, n (%)	281	84 (93.3)	163 (85.3)	0.06	220	94 (90.4)	100 (86.2)	0.34
Adm SBP (mm Hg)	267	104 ± 34	106 ± 36	0.74	208	102 ± 33	102 ± 33	0.86
Adm HR (bpm)	268	110 ± 30	111 ± 30	0.79	205	113 ± 29	114 ± 31	0.72
Adm BD	228	−12 ± 6	−10 ± 7	0.13	173	−11 ± 7	−11 ± 7	0.74
Adm INR	228	1.5 (1.2–2.0)	1.4 (1.2–1.7)	0.12	177	1.4 (1.2–1.9)	1.4 (1.2–1.8)	0.84
Adm temperature (°C)	254	36 (36–37)	36 (35–37)	0.27	201	36 (36–37)	36 (35–37)	0.26
Adm platelet (cells/mm^3)	183	188 (138–224)	215 (151–268)	0.005	145	197 (133–240)	219 (144–276)	0.03
Adm fibrinogen	256	143 (112–193)	158 (107–218)	0.59	203	148 (126–219)	135 (80–190)	0.06
Adm GCS	88	3 (3–12)	3 (3–10)	0.39	70	3 (3–11)	3 (3–10)	0.88
ISS	268	40 ± 13	40 ± 13	0.94	208	41 ± 12	42 ± 14	0.52
FFP (units)†	281	8 (4–12)	5 (2–8)	<0.001	220	11 (6–16)	8 (5–13)	0.01
PLT (units)†	281	10 (6–18)	0 (0–1)	<0.001	220	14.5 (12–22.5)	2 (0–5)	<0.001
RBC (units)†	281	12 (9–20)	9 (6–14)	<0.001	220	16.5 (12–23)	15 (12–23.5)	0.69
FFP:RBC ratio	281	0.57 (0.4–0.75)	0.53 (0.19–0.8)	0.05	220	0.58 (0.42–0.9)	0.55 (0.31–0.71)	0.02
PLT:RBC ratio	281	0.78 (0.6–1.2)	0.02 (0.01–0.1)	<0.001	220	0.86 (0.67–1.09)	0.11 (0.01–0.26)	<0.001
Cryoprecipitate (units)†	281	0 (0–10)	0 (0–0)	<0.001	220	3 (0–18)	0 (0–10)	0.009
Crystalloids (L)†	281	7.7 (5–11.4)	6.2 (4.5–10)	0.19	220	11.8 (7.6–15.6)	9.9 (6.6–15)	0.06
rFVIIa, n (%)	268	18 (20)	14 (7.4)	0.002	215	21 (21)	10 (8.7)	0.01

Adm, Admission; bpm, beats per minute; GCS, Glasgow Coma Score; rFVIIa, recombinant-activated factor VII; SBP, systolic blood pressure; TBI+, head AIS score ≥3.
* 6 h ratios for 5 units RBC/6-h group and 24 h ratios for 10 units RBC/24-h group.
† Units reported are 6 h totals for 5 units RBC/6-h group and 10 h totals for 10 units RBC/24-h group.
All statistics reported as mean ± SD, frequency (%), or median (IQR).

TBI+ patients, 526 TBI−, and 43 patients without head AIS scores available. For the 643 patients in the ≥10 RBC in 24-hour group, there were 220 TBI+, 402 TBI−, and 21 patients without head AIS scores available. Variables for these patient groups are described in Tables 1–4. For the patients in the ≥5 RBC in 6 hours and the ≥10 RBC in 24 hours groups (TBI+ and TBI−), the admission variables that were used to create a propensity score from a multivariate logistic regression model were base deficit (BD), heart rate (HR), and units of cryoprecipitate at 6 hours, which were significantly associated with having received a high:low platelet or plasma ratio (data not shown). The variables that were independently associated with 30-day mortality were age, admission BD and HR, Glasgow Coma Scale, Injury Severity Score (ISS), PLT:RBC (high or low), and FFP:RBC (high or low) (Tables 5–8).

Patients Transfused ≥5 Units of RBCs in First 6 Hours

TBI+

All admission variables compared between patients transfused a high and low ratio of PLT:RBC were similar except the admission platelet concentration (median [interquartile range {IQR}]) was significantly decreased, 188 (138–224) versus 215 (151–268), respectively ($p = 0.005$), for the group of patients transfused with an increased platelet ratio (Table 1). Patients who received a high and low FFP:RBC ratio were admitted with an increased BD, mean (±SD), −10 (±7) versus −12 (±6), respectively ($p = 0.04$), and a decreased admission temperature, 35.8°C (±1.5) versus 36.3°C (±1.2), respectively ($p = 0.007$) (Table 2). The high and low platelet ratio groups received a median (IQR) PLT:RBC ratio from 0 to 6 hours from admission of 0.78 (0.60–1.20) and 0.02 (0.01–0.1.00), respectively ($p < 0.001$), and the high and low plasma ratio groups an FFP:RBC ratio from 0 to 6 hours of 0.75 (0.62–1) and 0.25 (0.02–0.36), respectively ($p < 0.001$). Unadjusted 30-day survival was increased for patients transfused with a high ratio of PLT:RBC ($p = 0.01$) but was similar for patients transfused a high or low ratio of FFP:RBC ($p = 0.48$; Fig. 2). Upon propensity score adjustment, a high ratio of PLT:RBC was independently associated with increased 30-day survival with a hazard ratio (95% confidence interval) of 0.44 (0.27–0.70), ($p < 0.001$), whereas the FFP:RBC ratio was not associated with increased survival (Table 5). There was no significant association between cause of death and platelet ratio group (Table 9).

TBI−

All admission variables compared between patients transfused a high or low ratio of PLT:RBC were similar except the admission BD was higher and platelet concentration was lower for patients transfused an increased platelet ratio (Table 3). In addition, patients transfused a high PLT:RBC ratio were transfused an increased FFP:RBC ratio (Table 3). Patients who received a high FFP:RBC ratio were admitted with an increased admission HR and INR and were younger than those who received a low ratio (Table 4). In addition, patients transfused a high FFP:RBC ratio were

TABLE 2. Demographics on Admission for TBI+ Patients Receiving High and Low Plasma (FFP:RBC) Ratios*

	≥5 Units RBC/6 h				≥10 Units RBC/24 h			
Variables	**N**	**High**	**Low**	***p***	**N**	**High**	**Low**	***p***
Age (yr)	281	38 (25–54)	36.5 (25–57)	0.81	220	38 (25–55)	38 (26–58)	0.69
Male, n (%)	281	103 (65.6)	84 (67.7)	0.71	220	88 (64.7)	55 (65.5)	0.91
Blunt, n (%)	281	136 (86.6)	111 (89.5)	0.46	220	115 (84.6)	79 (94)	0.03
Adm SBP (mm Hg)	267	108 ± 35	102 ± 37	0.16	208	104 ± 33	99 ± 32	0.36
Adm HR (bpm)	268	109 ± 32	113 ± 28	0.23	205	113 ± 32	115 ± 26	0.58
Adm BD	228	−10 ± 7	−12 ± 6	0.04	173	−10 ± 7	−13 ± 6	0.02
Adm INR	228	1.4 (1.2–1.9)	1.38 (1.1–1.7)	0.09	177	1.5 (1.2–1.9)	1.4 (1.1–1.7)	0.14
Adm temperature (°C)	254	36 (35–36)	36 (36–37)	0.007	201	36 (35–37)	36 (36–37)	0.14
Adm platelet (cells/mm^3)	183	202 (146–256)	210 (144–254)	0.82	145	200 (135–253)	218 (158–266)	0.12
Adm fibrinogen	256	146 (105–202)	150 (112–207)	0.56	203	146 (104–186)	144 (112–276)	0.42
Adm GCS	88	3 (3–9)	3 (3–11)	0.41	70	3 (3–10)	3 (3–11)	0.61
ISS	268	41 ± 13	40 ± 14	0.91	208	40 ± 13	44 ± 12	0.04
FFP (units)†	281	8 (5–12)	2 (0–5.5)	<0.00	220	12 (9–18)	4.5 (3.5–8)	<0.001
PLT (units)†	281	2 (0–6)	0 (0–8)	0.49	220	6 (3–14.5)	6 (0–15)	0.13
RBC (units)†	281	10 (7–13)	10 (7–17.5)	0.23	220	15 (12–21)	17 (12–24)	0.58
FFP:RBC ratio	281	0.75 (0.62–1)	0.25 (0.02–0.36)	<0.001	220	0.71 (0.59–0.92)	0.31 (0.2–0.4)	<0.001
PLT:RBC ratio	281	0.13 (0.02–0.6)	0.02 (0.01–0.57)	0.1	220	0.5 (0.16–0.86)	0.34 (0.01–0.8)	0.04
Cryoprecipitate (units)†	281	0 (0–10)	0 (0–0)	0.02	220	1 (0–10)	0 (0–8)	0.05
Crystalloids (L)†	281	6.4 (4.5,10)	7.13 (4.8–11.25)	0.23	220	10.9 (7.5–15.1)	10.2 (5.4–17.3)	0.65
rFVIIa, n (%)	268	16 (10.3)	16 (12.9)	0.49	203	15 (11.2)	16 (19.8)	0.08

Adm, Admission; bpm, beats per minute; GCS, Glasgow Coma Score; rFVIIa, recombinant-activated factor VII; SBP, systolic blood pressure; TBI+, head AIS score ≥3.
* 6 h ratios for 5 units RBC/6-h group and 24 h ratios for 10 units RBC/24-h group.
† Units reported are 6 h totals for 5 units RBC/6-h group and 10 h totals for 10 units RBC/24-h group.
All statistics reported as mean ± SD, frequency (%), or median (IQR).

transfused an increased PLT:RBC ratio (Table 4). The high and low PLT ratio groups received a median (IQR) PLT:RBC ratio of 0.86 (0.64–1.11) and 0.02 (0.01–0.11), respectively ($p < 0.001$) and the high and low FFP ratio groups an FFP:RBC ratio of 0.7 (0.58–0.90) and 0.25 (0.02–0.38), respectively ($p < 0.001$). Unadjusted 30-day survival was increased ($p = 0.002$) for patients transfused an increased FFP:RBC ratio and was similar ($p = 0.4$) for patients transfused a high or low ratio of PLT:RBC (Fig. 2). Upon propensity score adjustment, a high ratio of FFP:RBC was independently associated with increased 30-day survival with a hazard ratio (95% confidence interval) of 0.63 (0.40–0.98) ($p = 0.04$), whereas a high or low PLT:RBC ratio was not associated with increased survival (Table 6). In this patient group, a high ratio of FFP:RBC was associated with a decreased risk of death from hemorrhage and increased risk of death from MOF (Table 10).

Patients Transfused 10 Units of RBC in 24 Hours

TBI+

All admission variables compared between patients transfused a high or low ratio of PLT:RBC were similar except the admission platelet concentration was lower for patients transfused an increased ratio of PLT (Table 1). Patients who received a high and low FFP:RBC ratio experienced a decreased risk of blunt injury (85% vs. 94%, respectively, $p = 0.03$), a decreased BD, −10.1 (±7.4) versus −12.6 (±6.1), respectively $p = 0.02$, and a lower ISS, 40.3 (±13.5) versus 44 (±12.5), respectively $p = 0.04$ (Table 2). Patients transfused a high PLT and FFP ratios were also transfused increased FFP and PLT ratios, respectively (Tables 1 and 2). The high and low PLT ratio groups received a median (IQR) PLT:RBC ratio of 0.65 (0.47–0.86) and 0.05 (0.01–0.2), respectively ($p < 0.001$) and the high and low FFP ratio groups an FFP:RBC ratio of 0.67 (0.53–0.92) and 0.29 (0.11–0.38), respectively ($p < 0.001$). Unadjusted 30-day survival was increased for patients transfused with increased PLT:RBC ratio and for patients transfused an increased FFP:RBC ratio (Fig. 3). Upon propensity score adjustment, high PLT:RBC ratio was independently associated with increased 30-day survival with a hazard ratio of 0.47 (0.27–0.82), ($p = 0.008$), whereas the high FFP:RBC ratio was not associated with increased survival (Table 7). Cause of death was not associated with PLT:RBC ratio group (Table 9).

TBI−

All admission variables compared between patients transfused a high or low ratio of PLT:RBC were similar except patient age, BD, and ISS (Table 3). Differences between patients transfused a high or low ratio of FFP:RBC included patient sex, admission HR, INR, and Glasgow Coma Scale (Table 4). The high and low PLT ratio groups received a median (IQR) PLT:RBC ratio of 0.65 (0.39–1.00) and 0.04 (0.01–0.20), respectively ($p < 0.001$) and the high and low FFP ratio groups an FFP:RBC ratio of 0.67 (0.50–0.86) and 0.29 (0.12–0.40), respectively ($p < 0.001$). Patients transfused a high PLT and FFP ratios were also transfused in-

TABLE 3. Demographics on Admission for TBI− Patients Receiving High and Low Platelet (PLT:RBC) Ratios*

	≥5 Units RBC/6 h				≥10 Units RBC/24 h			
Variables	**N**	**High**	**Low**	***p***	**N**	**High**	**Low**	***p***
Age (yr)	526	31 (23–46)	36 (25–48)	0.13	402	30 (23–46)	36 (26–49)	0.02
Male, n (%)	526	116 (79.5)	306 (80.5)	0.78	402	141 (79.2)	177 (79)	0.96
Blunt, n (%)	526	70 (47.9)	189 (49.7)	0.71	402	92 (51.7)	121 (54)	0.64
Adm SBP (mm Hg)	473	102 ± 31	106 ± 29	0.2	361	103 ± 33	103 ± 29	1
Adm HR (bpm)	493	115 ± 29	112 ± 27	0.41	372	118 ± 28	113 ± 27	0.08
Adm BD	418	−12 ± 7	−11 ± 6	0.05	335	−12 ± 7	−11 ± 7	0.04
Adm INR	403	1.3 (1.1–1.57)	1.3 (1.1–1.5)	0.37	325	1.3 (1.1–1.6)	1.3 (1.2–1.6)	0.8
Adm temperature (°C)	433	36 (36–37)	36 (36–37)	0.97	334	36 (36–37)	36 (35–36)	0.07
Adm platelet (cells/mm^3)	264	200 (140–244)	223 (152–281)	0.01	198	199 (139–251)	214 (138–268)	0.47
Adm fibrinogen	454	141 (98–205)	123 (80–178)	0.23	345	134 (80–201)	123 (89–168)	0.44
Adm GCS	159	14 (3–15)	14 (3–15)	0.69	131	14 (5–15)	14 (3–15)	0.22
ISS	502	26 ± 14	26 ± 16	0.73	380	26 ± 14	30 ± 16	0.008
FFP (units)†	526	8 (4–13)	4 (1–9)	<0.001	402	10.5 (7–20)	8 (4–14.5)	<0.001
PLT (units)†	526	12 (10–20)	0 (0–2)	<0.001	402	17 (12–30)	2 (0–6)	<0.001
RBC (units)†	526	14 (10–23)	10 (6–19)	<0.001	402	18 (12–29)	17 (12–28)	0.48
FFP:RBC ratio	526	0.58 (0.45–0.83)	0.44 (0.21–0.67)	<0.001	402	0.59 (0.42–0.8)	0.46 (0.27–0.67)	<0.001
PLT:RBC ratio	526	0.86 (0.66–1.09)	0.04 (0.01–0.32)	<0.001	402	0.83 (0.64–1.07)	0.1 (0.01–0.29)	<0.001
Cryoprecipitate (units)†	526	2 (0–10)	0 (0–0)	<0.001	402	6.5 (0–16)	0 (0–6)	<0.001
Crystalloids (L)†	526	8.1 (5.5–12)	7 (4–10)	<0.001	402	12.6 (8.3–19.35)	10 (6.29–16.15)	<0.001
rFVIIa, n (%)	501	30 (20.5)	27 (7.1)	<0.001	378	35 (19.8)	23 (10.4)	0.008

Adm, Admission; bpm, beats per minute; GCS, Glasgow Coma Score; rFVIIa, recombinant-activated factor VII; SBP, systolic blood pressure; TBI+, head AIS score ≥3.
* 6 h ratios for 5 units RBC/6-h group and 24 h ratios for 10 units RBC/24-h group.
† Units reported are 6 h totals for 5 units RBC/6-h group and 10 h totals for 10 units RBC/24-h group.
All statistics reported as mean ± SD, frequency (%), or median (IQR).

creased FFP and PLT ratios, respectively (Tables 3 and 4). Unadjusted 30-day survival was increased for patients transfused increased FFP:RBC ratio and was similar for patients transfused a high or low PLT:RBC ratio (Fig. 3). Upon propensity score adjustment, a high ratio of FFP:RBC was independently associated with increased 30-day survival with a hazard ratio of 0.56 (0.36−0.86) ($p = 0.008$), whereas an association between a high PLT:RBC ratio and survival approached significance with a hazard ratio of 0.63 (0.39, 1.04) ($p = 0.07$). In this patient group, a high ratio of FFP:RBC was associated with decreased risk of death from hemorrhage and increased risk of death from MOF (Table 10).

Additional Analyses

To determine whether survivorship bias was affecting results, data were reanalyzed after excluding patients who died <90 minutes and <120 minutes from hospital admission, with the same variables used in the propensity score. In general, the relationships were consistent with those already described (Table 11).

DISCUSSION

This is the first study to individually analyze associations between blood product ratios and mortality for TBI+ and TBI− patients. Our results in two differently defined cohorts of patients at high risk of mortality from traumatic injuries indicate that there is an independent association of improved survival for TBI+ patients transfused a high PLT:RBC ratio, in contrast to TBI− patients who benefit from a high plasma:RBC ratio. These results persisted even when we excluded patients who died within 90 minutes or 120 minutes from admission to compensate for possible survival bias. These results also strengthen our main results because they indicate that even when patients who die quickly from hemorrhage were excluded and should benefit the most from increased PLT and FFP transfusion, our results remained consistent.

Previous studies that report improved survival with the transfusion of increased platelet and plasma ratios for patients at high risk of death from traumatic injuries have not differentiated patients according to severe TBI status.[7,8,11,13] Two of these studies adjusted their results for other variables associated with survival.[8,13] As the risk of death from brain injury and hemorrhage is different for TBI+ and TBI− patients,[18] and BBB repair is required for TBI+ patients and may not be for TBI-patients, it is plausible that outcomes associated with increased PLT and FFP:RBC ratios may affect these two patient groups differently.

The retrospective nature of our report does not allow us to examine the potential mechanisms that support our findings. One theory is that BBB healing requires platelets for adequate repair. A recent study in rodents indicates that with BBB injury, platelets and not plasma activated oligodendrite precursor cells (OPCs).[30] The role of OPCs in the damaged central nervous system is to differentiate into oligodendrocytes and repair regions of demyelination.[30] The association between reactive behavior of OPCs, BBB breakdown and

TABLE 4. Demographics on Admission for TBI− Patients Receiving High and Low Plasma (FFP:RBC) Ratios*

	≥5 Units RBC/6 h				≥10 Units RBC/24 h			
Variables	**N**	**High**	**Low**	***p***	**N**	**High**	**Low**	***p***
Age (yr)	526	31 (23–46)	36 (25–48)	0.03	402	32 (23–49)	36 (26–48)	0.09
Male, n (%)	526	192 (81.4)	230 (79.3)	0.56	402	188 (83.2)	130 (73.9)	0.02
Blunt, n (%)	526	112 (47.5)	147 (50.7)	0.46	402	121 (53.5)	92 (52.3)	0.8
Adm SBP (mm Hg)	473	105 ± 30	104 ± 29	0.88	361	105 ± 32	100 ± 29	0.18
Adm HR (bpm)	493	117 ± 28	109 ± 26	0.002	372	118 ± 28	111 ± 26	0.03
Adm BD	418	−11 ± 6	−11 ± 7	0.71	335	−11 ± 7	−12 ± 7	0.29
Adm INR	403	1.4 (1.1–1.6)	1.3 (1.1–1.4)	0.008	325	1.4 (1.2–1.7)	1.3 (1.1–1.5)	0.04
Adm temperature (°C)	433	36 (36–37)	36 (36–37)	0.41	334	36 (35–37)	36 (36–37)	0.74
Adm platelet (cells/mm^3)	264	209 (149–272)	221 (146–273)	0.8	198	200 (136–267)	208 (142–254)	0.9
Adm fibrinogen	454	123 (91–198)	138 (80–184)	0.81	345	123 (81–185)	135 (80–186)	0.5
Adm GCS	159	14 (3–15)	15 (8–15)	0.08	131	14 (3–15)	14 (6–15)	0.09
ISS	502	27 ± 14	25 ± 16	0.39	380	28 ± 14	28 ± 16	0.97
FFP (units)†	526	8.5 (6–16)	2.5 (0–6)	<0.001	402	14 (9–22)	5 (3–8.5)	<0.001
PLT (units)†	526	4 (0–12)	0 (0–6)	<0.001	402	10 (4–18)	6 (0–12)	<0.001
RBC (units)†	526	11 (7–20)	10 (7–21)	0.49†	402	17 (12–30)	18.5 (12.5–28)	0.84
FFP:RBC ratio	526	0.7 (0.58–0.9)	0.25 (0.02–0.38)	<0.001	402	0.7 (0.58–0.9)	0.31 (0.19–0.4)	<0.001
PLT:RBC ratio	526	0.29 (0.02–0.75)	0.02 (0.01–0.38)	<0.001	402	0.5 (0.17–0.86)	0.2 (0.01–0.61)	<0.001
Cryoprecipitate (units)†	526	0 (0–10)	0 (0–0)	<0.001	402	3 (0–12)	0 (0–9)	<0.001
Crystalloids (L)†	526	7.1 (4.18–10.4)	7.24 (4.5–11)	0.51	402	12 (8–17.6)	11 (6–18.36)	0.14
rFVIIa, n (%)	501	26 (11.1)	31 (10.7)	0.9	378	33 (14.7)	25 (14.4)	0.93

Adm, Admission; bpm, beats per minute; GCS, Glasgow Coma Score; rFVIIa, recombinant-activated factor VII; SBP, systolic blood pressure; TBI+, head AIS score ≥3.
* 6 h ratios for 5 units RBC/6-h group and 24 h ratios for 10 units RBC/24-h group.
† Units reported are 6 h totals for 5 units RBC/6-h group and 10 h totals for 10 units RBC/24-h group.
All statistics reported as mean ± SD, frequency (%), or median (IQR).

TABLE 5. Propensity Score*-Adjusted Multivariate Cox Regression: Variables Associated With 30-d Mortality for the ≥5 Units RBC/6-h Group With TBI+

Variables	**Hazard Ratio (95% CI)**	***p***
ISS	1.03 (1.01–1.043)	0.001
GCS	0.94 (0.894–0.988)	0.02
PLT:RBC ratio group (high)	0.44 (0.272–0.703)	<0.001
FFP:RBC ratio group (high)	0.96 (0.642–1.428)	0.83

GCS, Glasgow Coma Score; TBI+, head AIS score ≥3.
* Platelet ratio (high/low) propensity score based on logistic model with admission platelets.
FFP ratio (high/low) propensity based on a logistic model with deficit and cryoprecipitate.

TABLE 6. Propensity Score*-Adjusted Multivariate Cox Regression: Variables Associated With 30-d Mortality for the ≥5 units RBC/6-h Group With TBI−

Variables	**Hazard Ratio (95% CI)**	***p***
Age	1.03 (1.017–1.042)	<0.001
ISS	1.04 (1.024–1.05)	<0.001
Admission BD	0.94 (0.907–0.968)	<0.001
PLT:RBC ratio group (high)	0.71 (0.436–1.171)	0.18
FFP:RBC ratio group (high)	0.63 (0.403–0.983)	0.04

GCS, Glasgow Coma Score; TBI+, head AIS score ≥3.
* Platelet Ratio (Hi/Lo) propensity score based on a logistic model with admission platelets.
FFP Ratio (Hi/Lo) propensity based on a logistic model with Heart rate and Cryoprecipitate.

inflammation, and the surveillance-like functions of OPCs imply a crucial mechanism linking OPCs (in a possibly protective role) with platelet-orchestrated healing and the inflammatory response to central nervous system injury.[30] In addition, recent laboratory studies have suggested that plasma restores the endothelial glycocalyx injured by hemorrhagic shock.[31] The glycocalyx is a network of soluble plasma components that projects from the endothelial cell surface and maintains membrane integrity.[32] It consists of proteoglycans and glycoproteins attached to the cell membrane, forming a protective barrier that protects against pathologic neutrophil-endothelial cell interactions. Although restitution of the glycocalyx by plasma may restore shock-induced endothelial dysfunction in the lung,[33] its role in the brain has not been studied.

Despite increased survival for TBI+ patients transfused a high ratio of PLT:RBCs, there was no difference in the cause of death for these patients compared with those transfused a low PLT:RBC ratio. This may have been limited by the broad categories of cause of death that were determined for this database or a limited number of patient deaths and inadequate power to analyze cause of death appropriately. Increased survival for TBI− patients transfused a high ratio of FFP:RBCs was noted to have decreased death from hemorrhage but increased death secondary to MOF. This is consistent with previous reports that do not differentiate patients according to severe TBI status.[6–8,13,34] The increased

TABLE 7. Propensity Score*-Adjusted Multivariate Cox Regression: Variables Associated With 30-d Mortality for the TBI+ and ≥10 RBC/24-h Group

Variables	Hazard Ratio (95% CI)	*p*
ISS	1.03 (1.013–1.05)	<0.001
GCS	0.94 (0.885–0.995)	0.03
Heart rate	0.99 (0.984–0.998)	0.02
PLT:RBC ratio group (high)	0.47 (0.269–0.822)	0.008
FFP:RBC ratio group (high)	1.18 (0.729–1.906)	0.5

GCS, Glasgow Coma Score; TBI+, head AIS score ≥3.

* Platelet ratio (high/low) propensity score based on a logistic model with mechanism of injury and admission platelets.

FFP ratio (high/low) propensity based on a logistic model with deficit and cryoprecipitate.

TABLE 8. Propensity Score*-Adjusted Multivariate Cox Regression: Variables Associated With 30-d Mortality for the TBI− and ≥10 RBC/24-h Group

Variables	Hazard Ratio (95% CI)	*p*
Age	1.02 (1.006–1.03)	0.003
ISS	1.03 (1.018–1.043)	<0.001
PLT:RBC ratio group (high)	0.63 (0.39–1.035)	0.07
FFP:RBC ratio group (high)	0.56 (0.361–0.86)	0.008

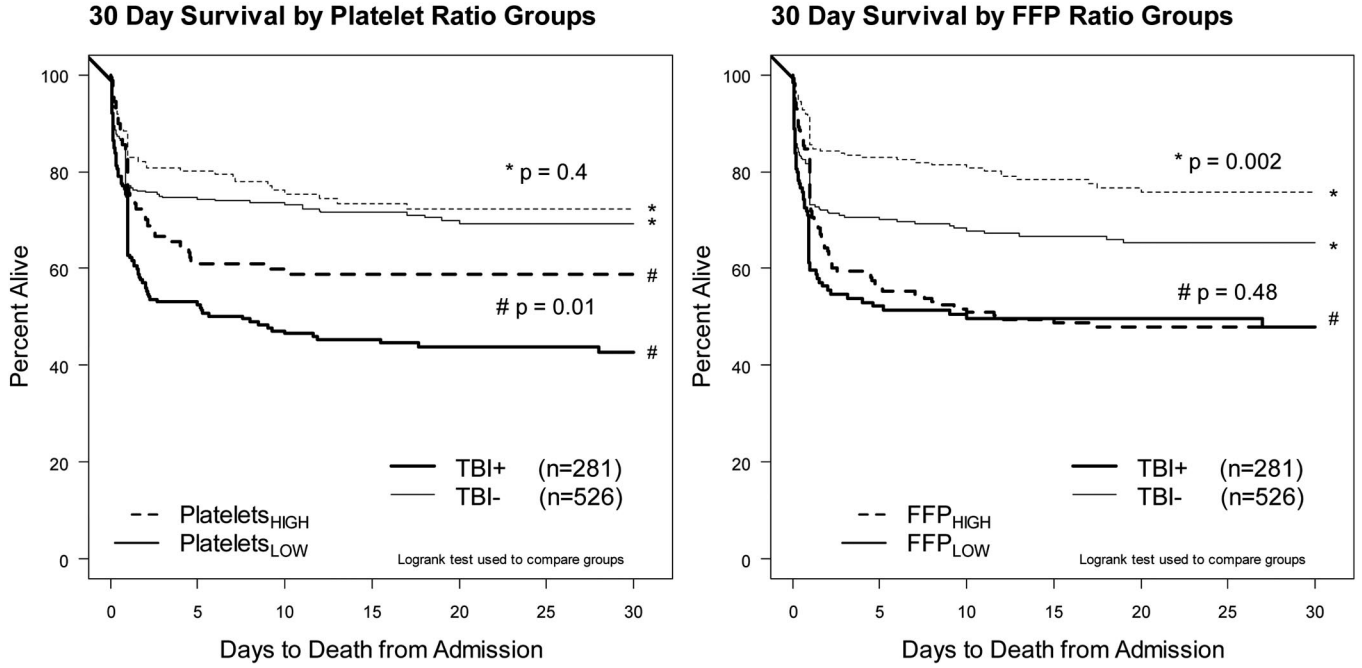
GCS, Glasgow Coma Score; TBI+, head AIS score ≥3.

* Platelet ratio (high/low) propensity score based on a logistic model with base deficit.

FFP ratio (high/low) propensity based on a logistic model with heart rate and cryoprecipitate units.

death from MOF is likely related to the increased survival in the high FFP:RBC ratio groups because they lived long enough to develop MOF, but it may also be related to the increased plasma transfusion.[33] Prospective studies of blood product ratios currently being performed will be able to more accurately determine the relationship between increased plasma transfusion and effects on mortality and MOF.

Initial studies of blood product ratios in trauma patients used one of the standard definitions of massive transfusion, 10 units of RBCs in 24 hours, to identify patients who are at high risk of death from hemorrhage.[6–8,13] A recent review that summarized blood product ratio studies[2] indicated that alternative blood product amounts (8–10 RBC units in 12 hours) and times from admission (3–12 hours) that ratios are measured[11,27–29] have also been used in an attempt to more accurately reflect the time from admission that patients are actively resuscitated and to decrease "catch up bias".[2] Patients who die from hemorrhage typically die within 6 hours,[24] and mortality increases in trauma patients after 5 units of RBCs have been transfused.[23] We analyzed two different patient groups (5 units of RBCs in 6 hours and 10 units of RBCs in 24 hours) that are at high risk of death to determine whether the time at which blood product ratios were measured affected our results. The two groups were similar in measures of severity of injury to include admission vital signs, laboratory values, ISS scores, and mortality rates and were further adjusted for in the propensity analyses. More importantly, our results were consistent between both groups of patients. Future research is needed to better define patients with massive bleeding at risk of death from hemor-



Abbreviations: Platelets $_{High}$, Platelet:RBC ≥ 1:2, Platelets $_{low}$, Platelet:RBC < 1:2; FFP $_{High}$, FFP:RBC ≥ 1:2, FFP $_{low}$, FFP:RBC < 1:2; TBI +, Head Abbreviated Injury Score ≥3; TBI-, Head Abbreviated Injury Score <3; min

Figure 2. Kaplan-Meier curves for the ≥5 units RBC in 6-hour groups.

TABLE 9. Cause of Death for TBI+ Patients Receiving High and Low Platelet (PLT:RBC) Ratios

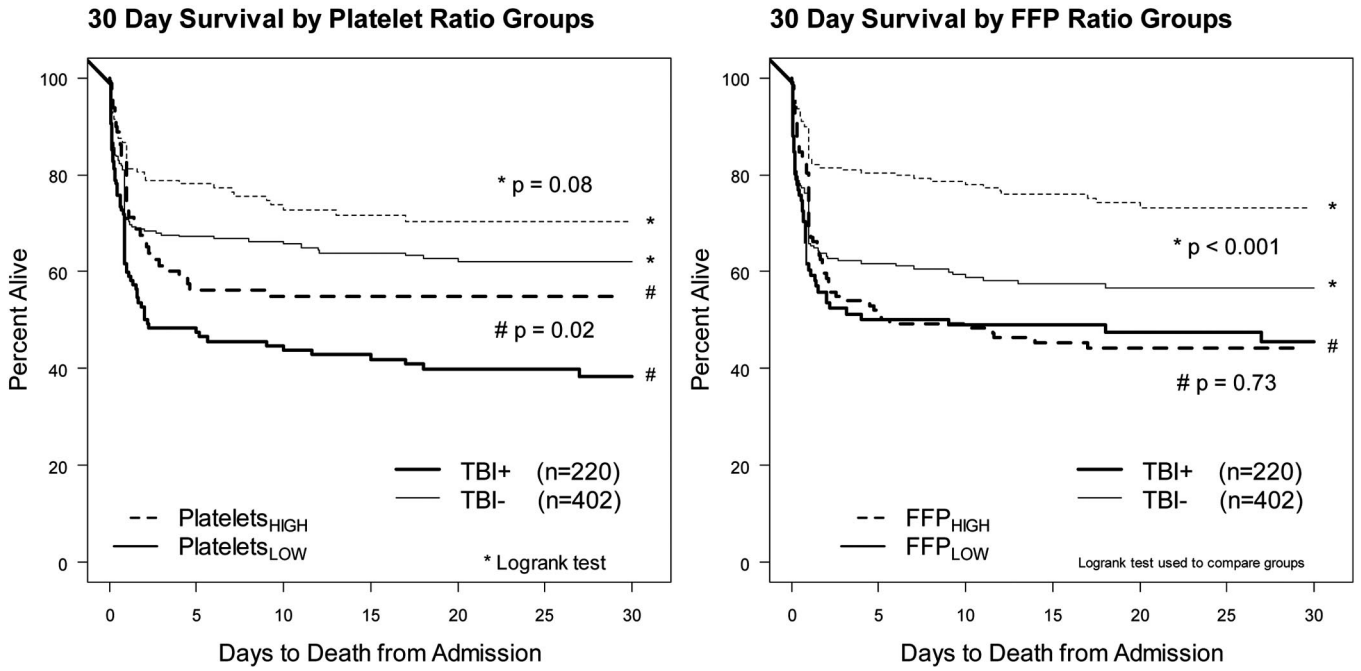
	≥5 Units RBC/6 h				≥10 Units RBC/24 h			
	N	High	Low	*p*	N	High	Low	*p*
Truncal hemorrhage, n (%)	136	10 (26.3)	31 (31.6)	0.54	113	12 (27.3)	29 (42)	0.11
Head injury, n (%)	141	25 (65.8)	68 (66)	0.98	115	29 (63)	39 (56.5)	0.49
MOF, n (%)	133	6 (16.7)	9 (9.3)	0.23	111	8 (19)	6 (8.7)	0.11
Other, n (%)	132	2 (5.6)	6 (6.3)	0.88	110	3 (7.1)	4 (5.9)	0.79

N, number of patients; TBI+, head AIS score ≥3.

TABLE 10. Cause of Death for TBI− Patients Receiving High and Low Plasma (FFP:RBC) Ratios

	≥5 Units RBC/6 h				≥10 Units RBC/24 h			
	N	High	Low	*p*	N	High	Low	*P*
Truncal hemorrhage, n (%)	140	34 (72.3)	82 (88.2)	0.02	128	34 (70.8)	71 (88.8)	0.01
Head injury, n (%)	128	4 (9.5)	5 (5.8)	0.44	118	3 (6.7)	5 (6.8)	0.97
MOF, n (%)	136	14 (29.8)	6 (6.7)	<0.001	126	16 (30.8)	4 (5.4)	<0.001
Other, n (%)	127	6 (14.6)	9 (10.5)	0.5	117	9 (20.5)	6 (8.2)	0.06

TBI−, head AIS score <3.



Abbreviations: Platelets $_{High}$, Platelet:RBC ≥ 1:2, Platelets $_{low}$, Platelet:RBC < 1:2; FFP $_{High}$, FFP:RBC ≥ 1:2, FFP $_{low}$, FFP:RBC < 1:2; TBI +, Head Abbreviated Injury Score ≥3; TBI-, Head Abbreviated Injury Score <3; min

Figure 3. Kaplan-Meier curves for the ≥10 untis RBC in 24-hour groups.

rhage rather than only studying patients who received a massive transfusion. The former approach will allow for analyzing patients based upon physiologic risk factors for hemorrhagic death, whereas the later is dependent upon the practitioners response to bleeding "ordering bias" and is limited by the capabilities of each treating facility, which both differ substantially from center to center. This ordering bias was well documented as a wide variability of transfusion ratios in a recent study by Holcomb et al.[7] that included 16 major US and British trauma centers over a 1-year period.

The limitations of this study include all of those inherent to retrospective studies to include selection bias and the potential for not adjusting for unmeasured variables. In addition, we did not adjust for center effect, which may have altered our results. The differences between study groups to include increased PLT ratio for the FFP ratio comparisons

TABLE 11. Propensity Score-Adjusted Multivariate Cox Regression for 30-d Mortality in Patient Groups That Exclude Those Who Died 90 and 120 Min After Hospital Admission

	High PLT:RBC Ratio		High FFP:RBC Ratio	
Patient Group	**Hazard Ratio (95% Confidence Interval)**	***p***	**Hazard Ratio (95% Confidence Interval)**	***p***
≥5 units/6 h, TBI+, 90 min, (n = 275)	0.44 (0.28–0.72)	<0.001	1 (0.67–1.5)	1
≥5 units/6 h, TBI−, 90 min, (n = 517)	0.73 (0.45–1.20)	0.22	0.65 (0.41–1.01)	0.06
≥10 units/24 h, TBI+, 90 min, (n = 217)	0.47 (0.27–0.82)	0.008	1.18 (0.73–1.90)	0.5
≥10 units/24 h, TBI−, 90 min, (n = 396)	0.66 (0.41–1.08)	0.1	0.59 (0.38–0.91)	0.02
≥5 units/6 h, TBI+, 120 min, (n = 270)	0.46 (0.28–0.74)	0.001	1.04 (0.69–1.57)	0.85
≥5 units/6 h, TBI−, 120 min, (n = 506)	0.77 (0.47–1.27)	0.31	0.66 (0.42–1.05)	0.08
≥10 units/24 h, TBI+, 120 min, (n = 213)	0.49 (0.28–0.87)	0.01	1.26 (0.77–2.05)	0.36
≥10 units/24 h, TBI−, 120 min, (n = 386)	0.7 (0.43–1.15)	0.16	0.61 (0.39–0.95)	0.03

TBI+, head AIS score ≥3; TBI−, head abbreviated injury score <3.

and increased FFP ratio for the PLT ratio comparisons are also a potential source for confounding. Even with the use of propensity score adjusted multivariate regression analysis, and the use of two separate scores to adjust for the effect of both ratios transfused, there may still be residual confounding present. Despite these important limitations, we analyzed a large sample of patients from 22 trauma centers throughout the United States and Great Britain. The patient groups were similar in most variables compared, and a sophisticated propensity analysis was used to adjust for the few differences between the groups compared and multivariate cox regression to adjust for factors associated with mortality. The consistency in our results between the two main study cohorts, and for the two alternative cohorts, also supports the validity of our results.

CONCLUSIONS

TBI+ patients transfused a high ratio of PLT:RBC and TBI− patients transfused a high ratio of FFP:RBC experienced improved 30-day survival. The differential effect of increased platelets and plasma on TBI+ and TBI− patients warrants further investigation in prospective studies. In addition, the standard definition of massive transfusion (10 units of RBCs in 24 hours) may not be optimal to determine inclusion criteria for studies examining associations between blood product transfusion and outcomes for patients at high risk of death secondary to traumatic hemorrhage. The analysis of patients transfused ≥5 units of RBCs in 6 hours may define a population that is of similar injury severity, risk of death, and more accurately reflects the blood products transfused during the active resuscitation period.

ACKNOWLEDGMENTS

We thank Joel Michalek, PhD, for his contributions to the statistical analysis and preparation of the manuscript. The authors wish to acknowledge the support of the numerous research coordinators at the various centers. This work was funded in part by a grant from the US Army to the University of Texas Health Science Center San Antonio, W81XWH-07-1-0717.

The additional authors are: (1) K. J. Brasel from the Medical College of Wisconsin, Milwaukee, WI; (2) G. Vercruysse and J. MacLeod from Emory University School of Medicine, Atlanta, GA; (3) R. P. Dutton from Maryland School of Medicine, Baltimore, MD; (4) J. C. Duchesne and N. E. McSwain from Tulane University, New Orleans, LA; (5) P. Muskat and J. Johannigamn from University Hospital, Cincinnati, OH; (6) H. M. Cryer and A. Tillou from University of California Los Angeles School of Medicine, Los Angeles, CA; (7) M. J. Cohen, J. F. Pittet, and P. Knudson from the University of California, San Francisco, CA; (8) M. A. De Moya from Massachusetts General Hospital, Boston, MA; (9) B. Tieu from Oregon Health Science Center, Portland, OR; (10) S. Brundage from Stanford University Medical Center, Stanford, CA; (11) L. M. Napolitano, M. Brunsvold, and K. C. Sihler from the University of Michigan Health System, Ann Arbor, MI; (12) G. Beilman from the University of Minnesota, Rochester, MN; (13) A. B. Peitzman, M. S. Zenait, J. Sperry, and L. Alarcon from the University of Pittsburg Medical Center, Pittsburg, PA; (14) M. A. Croce from the University of Tennessee Health Science Center, Memphis, TN; (15) J. P. Minei from University of Texas Southwestern Medical Center, Dallas, TX; (16) R. M. Stewart, S. M. Cohn, and J. E. Mickalek from the University of Texas Health Science Center, San Antonio, TX; (17) E. M. Bulger from the University of Washington, Seattle, WA; (18) B. A. Cotton and T. C. Nunez from Vanderbilt University Medical Center, Nashville, TN; (19) R. Ivatury from Virginia Commonwealth University, Richmond, VA; and (20) J. W. Meredith, P. Miller, G. J. Pomper, and B. Marin from Wake Forest University School of Medicine, Winston Salem, NC.

REFERENCES

1. McMullin NR, Holcomb JB, Sondeen J. Hemostatic resuscitation. In: Vincent J, ed. *Yearbook of Intensive Care and Emergency Medicine*. New York: Springer; 2006:265–278.
2. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev.* 2009;23:231–240.
3. Beekley AC. Damage control resuscitation: a sensible approach to the exsanguinating surgical patient. *Crit Care Med.* 2008;36(7 Suppl):S267–S274.
4. Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. *Transfusion.* 2006;46:685–686.

5. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma.* 2007; 62:307–310.
6. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma.* 2007;63:805–813.
7. Holcomb JB, Wade CE, Michalek JE. Increased plasma and platelet to RBC ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg.* 2008:447–458.
8. Perkins JG, Andrew CP, Spinella PC, et al. An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. *J Trauma*. 2009;66(4 Suppl):S77–S84; discussion S84–S75.
9. Duchesne JC, Hunt JP, Wahl G, et al. Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? *J Trauma.* 2008;65:272–276; discussion 276–278.
10. Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. *J Trauma.* 2009;66:693–697.
11. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma & platelets to packed red blood cells in the first six hours of massive transfusion improves outcomes in a large multi-center study. *Am J Surg*. 2009;197:565–570; discussion 570.
12. Cotton BA, Gunter OL, Isbell J, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma.* 2008;64:1177–1182; discussion 1182–1173.
13. Holcomb JB, Zarzabal LA, Michalek JE, et al. Increased platelet:RBC ratios are associated with improved survival after transfusion. *J Trauma*. 2011;71:S318–S328.
14. Wafaisade A, Lefering R, Tjardes T, et al. Acute coagulopathy in isolated blunt traumatic brain injury. *Neurocrit Care.* 2010;12:211–219.
15. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma.* 2003;54:1127–1130.
16. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. *Acta Neurochir (Wien).* 2008;150: 165–175; discussion 175.
17. Halpern CH, Reilly PM, Turtz AR, Stein SC. Traumatic coagulopathy: the effect of brain injury. *J Neurotrauma.* 2008;25:997–1001.
18. Gennarelli TA, Champion HR, Sacco WJ, Copes WS, Alves WM. Mortality of patients with head injury and extracranial injury treated in trauma centers. *J Trauma.* 1989;29:1193–1201; discussion 1201–1192.
19. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg.* 1998;186:528–533.
20. Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. *J Am Coll Surg.* 2004;198:20–26.
21. Snyder CW, Weinberg JA, McGwin G Jr, et al. The relationship of blood product ratio to mortality: survival benefit or survival bias? *J Trauma.* 2009;66:358–362; discussion 362–354.
22. Spinella PC, Perkins JG, Holcomb JB. RBC use and mortality at a US Army combat support hospital. *Crit Care Med.* 2007;35:A152(suppl).
23. Niles SE, McLaughlin DF, Perkins JG, et al. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma.* 2008;64:1459–1463; discussion 1463–1455.
24. Moore FA, Nelson T, McKinley BA, et al. Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. *J Trauma.* 2008;64:1010–1023.
25. Peng R, Chang C, Gilmore D, Bongard F. Epidemiology of immediate and early trauma deaths at an urban Level I trauma center. *Am Surg.* 1998;64:950–954.
26. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma.* 1995;38:185–193.
27. Kashuk JL, Moore EE, Johnson JL, et al. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? *J Trauma.* 2008;65:261–270; discussion 270–261.
28. Maegele M, Lefering R, Paffrath T, et al. Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. *Vox Sang.* 2008; 95:112–119.
29. Sperry JL, Ochoa JB, Gunn SR, et al. An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma.* 2008;65:986–993.
30. Rhodes KE, Raivich G, Fawcett JW. The injury response of oligodendrocyte precursor cells is induced by platelets, macrophages and inflammation-associated cytokines. *Neuroscience.* 2006;140:87–100.
31. Kozar RA, Zhang R, Holcomb JB, et al. Plasma Restoration of Endothelial Glycocalyx After Hemorrhagic Shock. *Shock.* 2009;31:S89.
32. Rehm M, Bruegger D, Christ F, et al. Shedding of the endothelial glycocalyx in patients undergoing major vascular surgery with global and regional ischemia. *Circulation.* 2007;116:1896–1906.
33. Pati S, Matijevik N, Doursout M, et al. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. *J Trauma*. 2010;69:S55–S63.
34. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma.* 2009;67:221–227; discussion 228–230.

