

An FFP:PRBC Transfusion Ratio $\geq 1:1.5$ Is Associated With A Lower Risk Of Mortality After Massive Transfusion

Jason L. Sperry, MD, MPH, Juan B. Ochoa, MD, Scott R. Gunn, MD, Louis H. Alarcon, MD, Joseph P. Minei, MD, Joseph Cuschieri, MD, Matthew R. Rosengart, MD, MPH, Ronald V. Maier, MD, Timothy R. Billiar, MD, Andrew B. Peitzman, MD, Ernest E. Moore, MD, and The Inflammation the Host Response to Injury Investigators

Objective: The detrimental effects of coagulopathy, hypothermia, and acidosis are well described as markers for mortality after traumatic hemorrhage. Recent military experience suggests that a high fresh frozen plasma (FFP):packed red blood cell (PRBC) transfusion ratio improves outcome; however, the appropriate ratio these transfusion products should be given remains to be established in a civilian trauma population.

Methods: Data were obtained from a multicenter prospective cohort study evaluating clinical outcomes in blunt injured adults with hemorrhagic shock. Those patients who required ≥ 8 units PRBCs within the first 12 hours postinjury were analyzed ($n = 415$).

Results: Patients who received transfusion products in $\geq 1:1.50$ FFP:PRBC ratio (high F:P ratio, $n = 102$) versus $<1:$

1.50 FFP:PRBC ratio (low F:P, $n = 313$) required significantly less blood transfusion at 24 hours (16 ± 9 units vs. 22 ± 17 units, $p = 0.001$). Crude mortality differences between the groups did not reach statistical significance (high F:P 28% vs. low F:P 35%, $p = 0.202$); however, there was a significant difference in early (24 hour) mortality (high F:P 3.9% vs. low F:P 12.8%, $p = 0.012$). Cox proportional hazard regression revealed that receiving a high F:P ratio was independently associated with 52% lower risk of mortality after adjusting for important confounders (HR 0.48, $p = 0.002$, 95% CI 0.3–0.8). A high F:P ratio was not associated with a higher risk of organ failure or nosocomial infection, however, was associated with almost a twofold higher risk of acute respiratory distress syndrome, after controlling for important confounders.

Conclusions: In patients requiring ≥ 8 units of blood after serious blunt injury, an FFP:PRBC transfusion ratio $\geq 1:1.5$ was associated with a significant lower risk of mortality but a higher risk of acute respiratory distress syndrome. The mortality risk reduction was most relevant to mortality within the first 48 hours from the time of injury. These results suggest that the mortality risk associated with an FFP:PRBC ratio $<1:1.5$ may occur early, possibly secondary to ongoing coagulopathy and hemorrhage. This analysis provides further justification for the prospective trial investigation into the optimal FFP:PRBC ratio required in massive transfusion practice.

Key Words: Massive transfusion, Transfusion ratio, Plasma, Cox proportional hazard regression.

J Trauma. 2008;65:986–993.

The effects of coagulopathy, hypothermia, and acidosis, touted as the “lethal triad,” are well-known markers for mortality after traumatic hemorrhage.^{1–4} Increasing attention has recently been paid to the correction of the coagulopathy that complicates massive transfusion and damage control resuscitation after severe injury.^{5–8} Importantly, coagulopathy has been shown to be present early after injury, at the time of trauma admission, even further substantiating the importance of early initiation of treatment and the prevention of coagulopathy.^{7,9–11} Both allogeneic blood and fresh frozen plasma (FFP) transfusions have been shown to be indepen-

dent risk factors for poor outcome in the critically ill.^{12–16} Despite these inherent risks, the acutely exsanguinating injured patient at times requires large volumes of these transfusion components until hemostasis can be obtained.^{17–19} Recent military experience suggests that, in patients who require massive transfusion, a high FFP: packed red blood cell (PRBC) transfusion ratio, in the first 24 hours postinjury, is associated with improved survival.²⁰ However, the appropriate ratio in which these transfusion products should be given remains controversial,²¹ and the associated risks attributable to a high FFP:PRBC transfusion ratio have not been adequately characterized for a civilian population.

Submitted for publication February 8, 2008.

Accepted for publication July 21, 2008.

Copyright © 2008 by Lippincott Williams & Wilkins

From the Division of General Surgery and Trauma, Departments of Surgery (J.L.S., J.B.O., L.H.A., M.R.R., T.R.B., A.B.P.) and Critical Care Medicine (S.R.G.), University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Division of Burn, Trauma, Critical Care (J.P.M.), Department of Surgery, University of Texas Southwestern Medical Center, Dallas, Texas; Division of General Surgery and Trauma (R.V.M.), Harborview Medical Center and the Department of Surgery, University of Washington, Seattle, Washington; and Department of Surgery (E.E.M.), Denver Health Medical Center and The University of Colorado Health Sciences Center, Aurora, Colorado.

This study was supported by funding from the National Institutes of Health (NIH NIGMS U54 GM062119-1).

Presented at the 38th Annual Meeting of the Western Trauma Association, February 24–March 1, 2008, Squaw Creek, Olympic Valley, California.

Address for reprints: Jason L. Sperry, MD, MPH, Division of General Surgery and Trauma, Department of Surgery, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213; email: sperryjl@upmc.edu.

DOI: 10.1097/TA.0b013e3181878028

The main objective of this current analysis was to determine whether $\geq 1:1.5$ FFP:PRBC transfusion ratio (high F:P ratio), in patients who required massive transfusion after injury, was associated with a lower risk of mortality. Additionally, the associated risks of multiple organ failure (MOF), nosocomial infection (NI), and acute respiratory distress syndrome (ARDS) attributable to high F:P transfusion ratio were independently characterized to determine whether those who survive their initial injury are at additional risk because of this type of transfusion practice. We hypothesized that patients who received a high F:P ratio would be at a lower risk of mortality, yet those who do survive, would have a higher risk of subsequent complications.

METHODS

Data were derived from the ongoing multicenter prospective cohort study known as the Inflammation and the Host Response to Injury Large Scale Collaborative Program (www.gluegrant.org) supported by the National Institute of General Medical Sciences (NIGMS), which is designed to characterize the genomic and proteomic response in injured patients at risk for MOF after traumatic injury and hemorrhagic shock.²² Standard operating procedures were developed and implemented across all institutional centers to minimize variation in postinjury care, including early goal directed resuscitation, strict glycemic control, venous thromboembolism prophylaxis, appropriate low tidal volume ventilation, ventilator-associated pneumonia management, and restrictive transfusion guidelines.²²⁻²⁷ Patients admitted to one of seven institutions, during a 3.5-year period (November 2003–March 2007), were included in the analysis. Inclusion criteria for the overall cohort study included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (≥ 6 meq/L), blood transfusion requirement within the first 12 hours, and any body region exclusive of the brain with an abbreviated injury score (AIS) ≥ 2 , allowing exclusion of patients with isolated traumatic brain injury. Patients younger than 16 years or older than 90 years and those with cervical spinal cord injury were also excluded from enrollment. For the current study, only patients who required ≥ 8 units of PRBCs within the first 12 hours from injury were included in the analysis. Clinical data were entered and stored in TrialDb, a web-based data collection platform, by trained research nurses.²⁸ Integrity of the data were maintained through ongoing curation and external data reviewed by an independent chart abstractor.

While patients were admitted to the intensive care unit (ICU), multiple organ dysfunction scores for renal, hepatic, cardiovascular, metabolic, hematologic, respiratory, and neurologic systems were determined daily.²⁹⁻³¹ All nosocomial infectious complications were monitored and recorded (infection type, culture specimen source, and bacteriology). The diagnosis of MOF required a maximum Marshall Multiple

Organ Dysfunction score >5 , whereas the diagnosis of NI required specific clinical criteria along with positive culture evidence. ARDS was defined as a PAO_2/FiO_2 ratio <200 , bilateral infiltrates on X-ray, a measured pulmonary artery occlusion pressure <18 mm Hg or the absence of clinical evidence for elevated left atrial pressure. All time variables to the respective outcome event were determined from the day of initial injury, whereas the time to the first NI was used in those patients with multiple infections. Diagnosis of a ventilator-associated pneumonia required a quantitative culture threshold of $\geq 10^4$ CFU/mL for bronchoalveolar lavage specimens.²⁴ Diagnosis of catheter-related blood stream infections required positive peripheral cultures with the identical organism obtained from either a positive semiquantitative culture (>15 CFU/segment), or positive quantitative culture ($>10^3$ CFU/segment) from a catheter segment specimen. Urinary tract infections required $>10^5$ organisms/mL of urine.

Each individual patients transfusion requirements for FFP and PRBCs (per unit) in the initial 12 hours after injury were used to determine an FFP:PRBC ratio. As this was a continuous variable, a specific cut point was required to categorize patients into the comparison groups (Fig. 1). Those patients who received at least an FFP:PRBC ratio of 1:1.50 were categorized as the high F:P ratio group. Patients who required an FFP:PRBC transfusion ratio of 1:1.51 or less were categorized as low F:P patients. Similar decimal place cutoffs ($\times .50$ – $\times .51$) were used for the stratified group analysis (see below).

Patients who received a high F:P ratio within the first 12 hours postinjury versus those patients who received a low F:P ratio were compared in a univariate fashion, and crude rates for mortality (in hospital), MOF ARDS and the development of NI were then determined and compared. The FFP:PRBC variable, specifically the low F:P group, was then categorized as 1:2 (1:1.51–1:2.50, $n = 105$), 1:3 to 4 (1:2.51–1:4.50, $n = 111$), and $\leq 1:5$ ($\leq 1:4.51$, $n = 97$) groups, and the time course of mortality risk associated with the FFP:PRBC transfusion ratio groups was characterized using Kaplan-Meier survival analysis. Cox proportional hazard regression modeling was then used to characterize the independent risk of mortality (in hospital) associated with a high F:P ratio relative

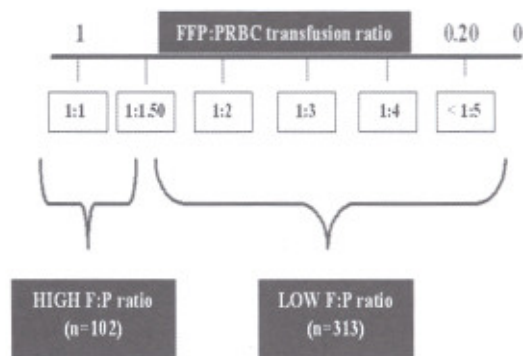


Fig. 1. FFP:PRBC group stratification.

to patients who received a low F:P ratio, after adjusting for important confounders. Then after stratification of the low F:P group, a similar regression analysis was performed. Confounders for the multivariate models were chosen to adjust for differences in injury characteristics, shock severity, operative and ICU interventions, and important comorbidities. Particular attention was paid to those factors that would alter the early coagulation status of the patient. Confounders for the final regression model included patient age, gender, Injury Severity Score (ISS), acute physiology and chronic health evaluation (APACHE) II score, presenting Glasgow Coma Score (GCS) and head AIS score, crystalloid, platelet and cryoprecipitate requirements (within 12 hours postinjury), worst base deficit and blood gas pH in the first 12 hours, lowest core body temperature, initial coagulation status (international normalized ratio [INR]), the requirement of early operative intervention (exploratory laparotomy or thoracotomy or sternotomy), early vasopressor (<24 hours) requirements, and a history of liver disease. Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

Cox proportional hazard regression was then also used to determine the independent associated risks of MOF, ARDS, and NI attributable to a high F:P ratio after controlling for important confounders. Patients who died or who were discharged from the hospital without a respective outcome event were censored, thus adjusting for any effect of early death on subsequent MOF, ARDS, and NI calculated risks.

All data were summarized as mean $\pm$ SD, median (interquartile range), or percentage (%). Student's *t* or Mann-Whitney statistical tests were used to compare continuous variables, whereas χ^2 or Fisher's exact tests were used for categorical variables. The institutional review board of each participating center approved the cohort study, while the institutional review board at the University of Pittsburgh Medical Center approved this current analysis.

RESULTS

Of the 1,036 blunt injured patients enrolled during the study period, 415 patients had a blood transfusion requirement of ≥ 8 units within the initial 12 hours after injury, and constituted the study population. In this cohort, 39 patients received no FFP within the first 12 hours from injury (FFP:PRBC ratio = 0) despite having a ≥ 8 unit blood transfusion requirement. The overall mortality for the study population was 33.5%, whereas the overall complication rates for MOF, NI, and ARDS were 56.4%, 46.5%, and 29.6%, respectively. This cohort of patients requiring massive transfusion had a median age of 41 years (IQR 25–54) and were significantly injured with a median ISS of 34 (IQR 22–43). An early (with 48 hours) exploratory laparotomy was required in 63% of patients, whereas 16% required an early thoracotomy or sternotomy. The median blood transfusion requirement in first 12 hours postinjury was 14 units (IQR 14–22) for the entire study cohort.

Those patients who received a high F:P ratio when compared with those who received a low F:P ratio were similar in age, gender, mechanism of injury, presenting base deficit and INR, level of acidosis, and prehospital comorbidities (Table 1). Those who received a high F:P ratio had higher ISS score and extremity AIS scores, higher APACHE II scores, lower GCS scores, and had lower nadir core body temperature measurements in the first 24 hours postinjury. They also had greater length of stay, ICU, and ventilator requirements; however, these comparisons would be inaccurate if an early mortality difference existed between the two groups. Hospital free days, ICU free days, and ventilator free days were compared with adjust for any such difference and confirmed that high F:P ratio patients had fewer hospital, ICU, and ventilator free days. Although not statistically different, high F:P ratio patients were less likely to undergo early laparotomy and had clinically higher head AIS scores. Crude rate comparison for mortality did not reach statistical significance, but high F:P ratio patients did have a significantly higher incidence of NI and ARDS, whereas a clear trend existed for having a higher rate of MOF (Table 2). Although no statistical differences in mortality were found between those who received a high F:P ratio versus those who did not, the clinically relevant difference in crude mortality between the comparison groups highlights the importance of the use of Cox proportional hazard regression, which allows patients who die before a respective outcome event to be appropriately censored, when determining complication risks.

Transfusion and resuscitation requirements compared across the two groups revealed that those who received a high F:P ratio had a reduced blood transfusion requirement at both 12 hours and 24 hours postinjury (Table 3). A significantly higher amount of cryoprecipitate was also given to the high F:P group; however, no differences were found in platelet or crystalloid administration. It is apparent that the vast majority of transfusion products and crystalloid were given within the first 12 hours after injury as the average requirements increased only slightly when analyzed at 24 hours out from injury.

Kaplan-Meier time to event analysis revealed early separation of survival curves for high F:P ratio patients relative to those who received a low F:P ratio (Fig. 2). Although the survival curves overall were not statistically different (log-rank: $p = 0.119$), the mortality rate at day 1 postinjury was significantly lower in the high F:P group (3.9% vs. 12.8%, $p = 0.012$). Although underpowered to be statistically different, when the FFP:PRBC variable was stratified into groups (high F:P, 1:2, 1:3–4, and $\leq 1:5$), similar findings with early separation of the survival curves are apparent at day 1 postinjury, with a dose response being demonstrated, based on the transfused FFP:PRBC ratio (Fig. 3).

Cox proportional hazard regression revealed that a high F:P ratio, relative to patients who received a low F:P ratio, was independently associated with a 52% lower risk of mortality (HR 0.48, $p = 0.002$, 95% CI 0.3–0.8), after controlling for important confounders. To verify that this finding held true irrespective of the amount of blood transfusion a patient

Table 1 Baseline Demographics and Characteristics for Patients Who Received a High F:P vs. a Low F:P Transfusion Ratio

	High F:P (n = 102)	Low F:P (n = 313)	p
Age (yrs)	41.1 ± 19	41.6 ± 18	0.805
Gender (%male)	76.5	68.4	0.120
Mechanism of injury (%)			
MVC	65.8	69.5	0.546
Ped struck	22.5	18.0	
Fall	5.0	6.1	
Other	6.7	6.4	
Initial base deficit (meq/L)	10.8 ± 5	10.7 ± 5	0.824
APACHE II score	33.6 ± 6	32.0 ± 6	0.021*
ED GCS score <8	69.6%	54.3%	0.007*
Injury severity score	36.5 ± 16	32.8 ± 14	0.029*
Maximum head AIS	1.6 ± 2	1.3 ± 2	0.064
Maximum chest AIS	3.7 ± 1	3.5 ± 1	0.135
Maximum abdomen AIS	3.3 ± 1	3.3 ± 1	0.925
Maximum extremities AIS	3.5 ± 1	3.1 ± 1	0.001*
Maximum spine AIS	2.2 ± 1	2.2 ± 1	0.634
24 h Lowest temp (°C)	34.1 ± 1	34.5 ± 2	0.016*
24 h Lowest blood gas pH	7.14 ± 0.1	7.13 ± 0.1	0.452
ED INR	1.89 ± 1	1.76 ± 2	0.453
24 h vasopressor requirement (%)	25.5	25.6	0.989
Early exploratory laparotomy (%)	55.8	65.8	0.060
Early thoracotomy/sternotomy (%)	15.7	16.7	0.808
Length of stay (days)	27.5 ± 25	20.7 ± 18	0.004*
ICU days	17.0 ± 18	13.2 ± 12	0.025*
Ventilator days	13.8 ± 17	10.8 ± 11	0.047*
Hospital free days [†]	38 (19–51)	42 (30–56)	0.008*
ICU free days [‡]	18 (5–25)	21 (12–27)	0.010*
Ventilator free days [‡]	22 (8–26)	23 (15–28)	0.008*
History of HTN (%)	10.8	13.4	0.489
History of MI (%)	4.2	1.4	0.075
History of COPD (%)	2.9	4.2	0.581
History of CHF (%)	0	1.9	0.159
History of DM (%)	8.8	6.1	0.336
History of liver disease (%)	6.9	8.0	0.712

* Statistically significant.

[†] Reported as median (interquartile range) relative to 60 d.[‡] Reported as median (interquartile range) relative to 30 d.

MVC, motor vehicle collision; ED, emergency department; Early, within 48 h postinjury; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; DM, diabetes mellitus.

Table 2 Crude Complication Rate Comparison for Patients Who Received a High F:P vs. a Low F:P Transfusion Ratio

	High F:P (n = 102)	Low F:P (n = 313)	p
Mortality (%)	28.4	35.1	0.212
MOF (%)	63.7	54.0	0.085
Nosocomial infection (%)	58.4	43.2	0.008*
ARDS (%)	47.1	24.0	0.001*

Marshall multiple organ failure dysfunction score >5.

required, the amount of blood (per unit) required at 12 hours postinjury was added as a covariate and the hazard ratio for high F:P ratio patients remained significant with the protective effect for mortality being unaltered (HR 0.57, $p = 0.026$, 95% CI 0.35–0.93). When complications including MOF and

Table 3 Transfusion Requirements at 12 h and 24 h Postinjury

	High F:P (n = 102)	Low F:P (n = 313)	p
12 h Postinjury			
Blood (unit)	14.3 ± 7	20.5 ± 15	0.001*
Fresh frozen plasma (unit)	14.0 ± 7	6.8 ± 7	0.001*
Crystalloid (L)	15.5 ± 7	15.3 ± 8	0.798
Platelet (unit)	1.4 ± 1	1.3 ± 2	0.744
Cryoprecipitate (unit)	3.2 ± 4	2.0 ± 4	0.006*
24 h Postinjury			
Blood (unit)	16.0 ± 9	22.0 ± 17	0.001*
Fresh frozen plasma (unit)	15.2 ± 9	7.6 ± 9	0.001*
Crystalloid (L)	18.8 ± 9	18.7 ± 11	0.892
Platelet (unit)	1.8 ± 2	1.6 ± 2	0.525
Cryoprecipitate (unit)	3.3 ± 4	2.3 ± 4	0.030*

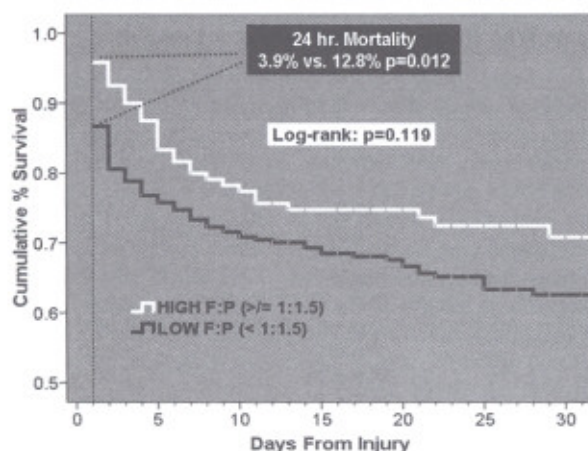


Fig. 2. Kaplan-Meier survival analysis comparing high F:P and low F:P transfusion ratios.

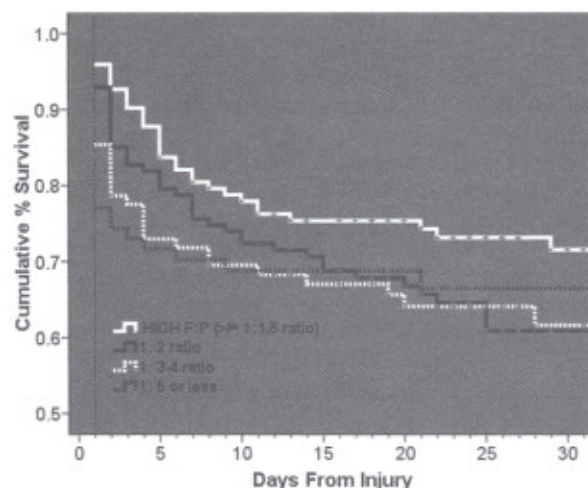


Fig. 3. Kaplan-Meier survival analysis comparing stratified FFP:PRBC transfusion ratio groups.

the development of NI were added to the model, no changes occurred and the hazard ratio for a high F:P ratio also remained unaltered, suggesting that these findings are not attributable to the development of these clinically outcomes. Similar to the results from the Kaplan-Meier analysis, when patients who died within the first 48 hours postinjury were excluded, the hazard ratio for a high F:P ratio became non-significant (HR 0.70, $p = 0.241$, 95% CI 0.4–1.2), indicating that, in part, the protective effect associated with a high F:P ratio was relevant to mortality early after injury, within the first 48 hours. Interestingly, when only patients who received ≥ 4 and < 8 units of blood ($n = 307$) were included in the model, the protective effects associated with a high F:P ratio were no longer present (HR 0.95, $p = 0.894$, 95% CI 0.4–2.0), suggesting that these findings hold true only when a patient requires massive transfusion. When the FFP:PRBC ratio was further stratified into

groups (high F:P, 1:2, 1:3–4, and $\leq 1:5$), relative to patients who received $< 1:5$ FFP:PRBC ratio, the hazard ratios for mortality also demonstrated a dose response relationship with a high F:P ratio remaining a significant independent predictor of survival (mortality HR 0.38, $p = 0.002$, 95% CI 0.2–0.7, Fig. 4).

To determine the potential risks associated with the proportion of FFP and PRBCs a patient receives, Cox proportional hazard regression was also used to determine the independent associated risks for MOF, NI, and ARDS attributable to receiving a high F:P ratio relative to a low F:P ratio. After controlling for differences in age, gender, injury severity, initial base deficit, and APACHE II score, a high F:P ratio was not significantly associated with a higher risk of MOF or NI (Fig. 5). However, a high F:P ratio was associated with almost a twofold higher risk of ARDS, after controlling for important confounders (Table 4). Finally, to characterize the time course at which this higher risk of ARDS occurs after injury, Kaplan-Meier analysis revealed significantly different (log rank: $p = 0.001$) (Fig. 6) time to event curves with separation around day 4 postinjury, signifying that this higher risk of pulmonary complications occurs soon after injury and were not a delayed outcome effect.

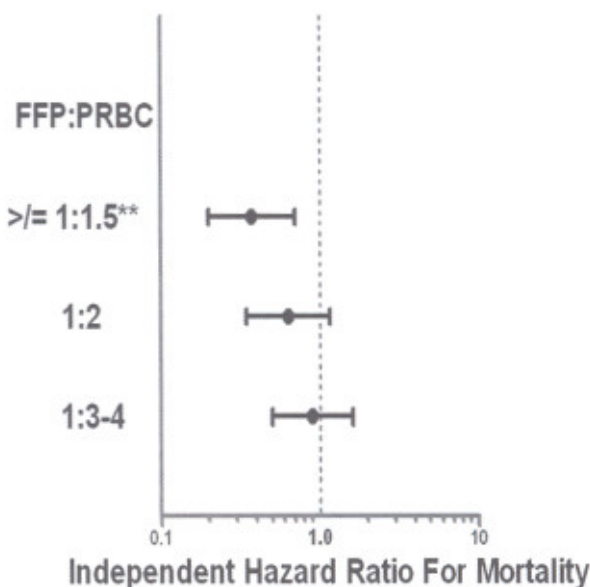


Fig. 4. Independent risk of mortality associated with stratified FFP:PRBC transfusion ratios using Cox proportional hazard regression modeling (relative to a FFP:PRBC $< 1:5$). Additional covariates included in the regression model: age, gender, Injury Severity Score, APACHE II score, ED Glasgow Coma Score and head AIS, 12 hour crystalloid, platelet and cryoprecipitate requirements, worst base deficit, and blood gas pH in the first 12 hours, lowest core body temperature in 24 hours, ED coagulation status (INR), the requirement of early operative intervention (exploratory laparotomy or thoracotomy or sternotomy), early vasopressor (< 24 hours) requirements, and a history of liver disease.

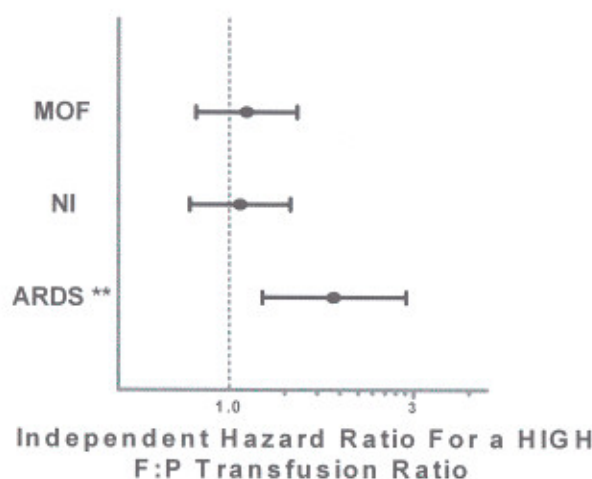


Fig. 5. Risk of complications associated with a high F:P ($\geq 1:1.5$) transfusion ratio.

Table 4 Cox Proportional Hazard Regression Model With ARDS as Dependent Variable

Outcome: ARDS	Hazard Ratio	p	95% CI
High F:P ratio	1.93	0.004	1.23–3.02
Gender	0.68	0.137	0.40–1.13
Age	0.99	0.748	0.99–1.01
ISS (25–1)*	1.07	0.850	0.51–2.25
ISS (≥ 42)*	1.60	0.249	0.72–3.59
APACHE II score	1.08	0.001	1.03–1.13
Initial base deficit	1.02	0.397	0.97–1.07
Maximum chest AIS score	1.01	0.981	0.79–1.27
24 h Crystalloid requirement	1.03	0.003	1.01–1.06

* Relative to ISS score of 1–24.

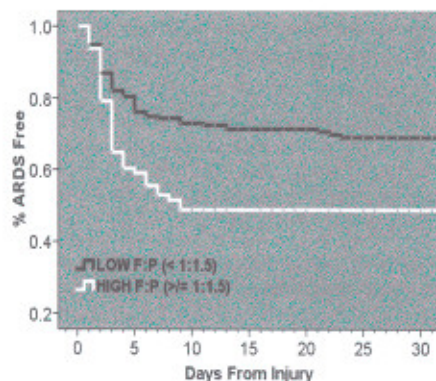


Fig. 6. Kaplan-Meier time to event analysis for the development of ARDS for high F:P and low F:P transfusion ratios.

DISCUSSION

Despite the significant advances in trauma care delivery and postinjury management practices that have occurred during the last decade, uncontrolled hemorrhage remains one of the leading causes of trauma-related deaths.^{4,32–34} A significant

amount of attention has been paid recently to the prevention and early treatment of the coagulopathy that complicates severe injury and damage control resuscitation.^{6,19,35,36} Historically, postinjury coagulopathy was thought to be a secondary event, resulting from resuscitative hemodilution, ongoing acidosis, and iatrogenic hypothermia.^{1,2,4} Recent evidence suggests that coagulopathy should be thought of as a primary event, as it occurs early after injury, even at the time of admission before major volume resuscitation, and is independently associated with detrimental outcomes.^{7,9–11} Recent military experience has provided strong evidence for a survival benefit associated with a high FFP:PRBC transfusion ratio (median, 1:1.4) in patients who require massive transfusion.²⁰ This cohort of military patients were primarily injured via a penetrating mechanism, had a median age of 24 years, and were predominantly men. The survival benefit was most pertinent to mortality that occurred within the first 4 hours from injury, primarily decreasing early death from ongoing hemorrhage.

The results of this current analysis complement these prior findings and verifies that a high F:P ($\leq 1:1.5$ FFP:PRBC) ratio is associated with a lower risk of mortality in a civilian population, who were somewhat older, were more typically split across gender, and who all had a blunt mechanism of injury. Similarly, these current results suggest that the protective effects associated with a high F:P ratio were most relevant to mortality within 48 hours from the time of injury, suggesting that the higher mortality risk associated with an FFP:PRBC transfusion ratio $< 1:1.5$ occurs earlier, possibly secondary to ongoing coagulopathy and uncontrollable hemorrhage. Despite crude mortality rates between the comparison groups not reaching statistical difference, the significant early mortality differences (within first 24 hours) was likely responsible for this overall mortality risk reduction. These protective effects were not found in those who required < 8 units of blood in the initial 12 hours from injury, and verifies that it is the massive transfusion population where prevention and early correction of coagulopathy seems most efficacious. These results add to our current understanding of the benefits associated with aggressive prevention and treatment of coagulopathy after injury and massive transfusion and additionally offers insight into the potential complications and risks attributable to this type of resuscitative practice.

Despite high F:P ratio patients having higher crude rates of NI, ARDS, and a trend toward a higher rate of MOF, after controlling for important confounders, there was no greater risk of MOF and NI attributable to a high F:P ratio found in multivariate regression analysis. These findings were apparent even though high F:P patients had a significantly greater hospital length of stay, higher ICU days, and more time required on the ventilator. Importantly, these length of stay differences were not simply due to a higher mortality rate in the low F:P ratio groups as hospital, ICU, and ventilator free days were also found to be less in the high F:P group. An

almost twofold greater independent risk of ARDS, however, was found to be attributable to high F:P ratio. This finding was independent of the quantity of crystalloid a patient received and the severity of chest injury sustained. This greater risk was apparent very early in the patients hospital course, within 4 days from the time of injury, temporally related to the transfusion product administration rather than a delayed outcome event. In a recent publication by Khan et al.,¹⁶ FFP and platelet transfusions were found to be independent risk factors for acute lung injury and ARDS, each having a higher risk relative to PRBC transfusion in critically ill medical patients. Exclusive of this study, a relative paucity of high-level evidence exists on the potential benefits or risks associated with transfusion products other than blood, particularly after injury.^{37,38} As this represents the first analysis to characterize the risks associated with a high FFP:PRBC ratio, further studies are required to verify these findings and to advance our understanding and insight into the risks associated with plasma-rich transfusion products (FFP, platelets, and cryoprecipitate) and the proportion in which they are and should be given with blood transfusions after injury.

It is intriguing that a lower risk of mortality was still demonstrated for those who received a high F:P ratio, despite these patients being more severely injured by ISS, having higher APACHE II scores, and lower GCS scores at admission. Similarly, the blood transfusion requirement, beginning as early as 12 hours postinjury, is unexpectedly lower in the high F:P patients based on these same group differences. Importantly, the protective effect attributable to a high FFP:PRBC was independent of the amount of blood transfusion required. This suggests that our findings were not due to differences in blood transfusion between the comparison groups and were most strongly dependent on the proportion of FFP relative to PRBC's a patient received. This analysis represents one of the largest that has analyzed transfusion product ratios in patients who require massive transfusion, but the secondary nature of this current analysis is unable to definitively prove that a high F:P ratio is causally responsible for these findings. Despite this limitation, proposed criteria³⁹ including consistency across different data sets, theoretical plausibility, the temporal relationship of the associations, the dose-response relationship in early survival, and finally the strength of the associations even after controlling for important confounders, does give precedence to the causality argument and justifies future higher level, prospective analyses, to provide more definitive answers concerning a high FFP:PRBC transfusion practice.

This analysis does have several potential limitations. First, this study is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response after severe injury and hemorrhagic shock. As with any secondary analysis, data were not recorded to answer our specific hypothesis stated for this study. Potential unknown or unmeasured confounding variables may be responsible for the associations described and the conclusions formulated. Factor VIIa use was not originally a data point recorded for

the overall cohort analysis. As its use and relevance has increased after injury, it was added as an important variable to be recorded but this prospectively occurred only as recently as December 2006. The data analyzed included patients upto April 2007. The use of factor VIIa in this small subset of patients was not different (high F:P-0% vs. low F:P-1%, $p = 0.326$) from those in whom prospectively recorded data exist; however, this represents incomplete data, and differences in factor VIIa use may be an important confounder and represents a significant limitation of this analysis. Despite similar comparison group characteristics overall and adjustment for differences that were apparent using multivariate regression analysis, patients who received a high F:P ratio soon after injury may be an inherently different population relative to those who received a low F:P ratio, as they were not randomized. Those patients who received a high F:P ratio were clinically less likely to undergo exploratory laparotomy (56% vs. 66% $p = 0.060$) and our results could be biased despite adjusting for this potential confounder in our regression models. Finally, the time of death (in hours) during the initial days of injury was not prospectively recorded in the data set. It may be that those patients most likely to die early due to uncontrolled hemorrhage were less likely to receive greater amounts of FFP secondary to time restraints or other unknown factors. However, all analyzed patients received at least 8 units of PRBC's within the first 12 hours from the time of injury, and those who received a low F:P ratio were given even greater amounts of blood at 12 hours and 24 hours, making any potential time to death difference between the comparison groups a less likely confounder.

In conclusion, patients who received an FFP:PRBC transfusion ratio $\geq 1:1.5$, relative to patients who received $<1:1.51$ FFP:PRBC ratio, had a significant lower risk of in-hospital mortality following massive transfusion after controlling for important confounders. This protective effect was most pertinent for mortality within the first 48 hours after injury and was independent of the blood transfusion requirement each individual patient received. Although crude mortality differences between the high F:P and low F:P groups did not reach statistical significance, the significant difference in early (24 hour) mortality was likely responsible for this overall mortality risk reduction. As the FFP:PRBC ratio became smaller (less FFP relative to PRBCs) a dose-response relationship was demonstrated for mortality, with those patients who received minimal or no FFP having the highest early mortality. Those who survived their initial injury were almost at a twofold higher risk of ARDS, independent of important confounders. These results suggest that the mortality risk associated with an FFP:PRBC transfusion ratio $<1:1.5$ may be secondary to inadequate correction of coagulopathy and uncontrollable hemorrhage. Patients who receive $\geq 1:1.5$ FFP:PRBC transfusion ratio and survive their initial injury are almost at a twofold higher risk of ARDS. This analysis provides further justification for the prospective trial investigation to evaluate the safety and efficacy of the incorporation of a high FFP:PRBC into massive transfusion practice.

REFERENCES

- Ferrara A, MacArthur JD, Wright HK, et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg*. 1990;160:515-518.
- Moore EE, Thomas G. Orr Memorial Lecture. Staged laparotomy for the hypothermia, acidosis, and coagulopathy syndrome. *Am J Surg*. 1996;172:405-410.
- Wilson RF, Dulchavsky SA, Soulier G, et al. Problems with 20 or more blood transfusions in 24 hours. *Am Surg*. 1987;53:410-417.
- Gentilello LM, Pierson DJ. Trauma critical care. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):604-607.
- Ho AM, Karmakar MK, Dion PW. Are we giving enough coagulation factors during major trauma resuscitation? *Am J Surg*. 2005;190:479-484.
- Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62:307-310.
- MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. *J Trauma*. 2003;55:39-44.
- Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. *World J Surg*. 2007;31:1055-1064.
- Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. *J Trauma*. 2003;54:1127-1130.
- Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma*. 2007;62:112-119.
- Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *J Trauma*. 2003;54:454-463.
- Claridge JA, Sawyer RG, Schulman AM, et al. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *Am Surg*. 2002;68:566-572.
- Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma*. 2003;54:898-905; discussion 905-897.
- Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg*. 1997;132:620-624; discussion 624-625.
- Robinson WP III, Ahn J, Stiffler A, et al. Blood transfusion is an independent predictor of increased mortality in nonoperatively managed blunt hepatic and splenic injuries. *J Trauma*. 2005;58:437-444; discussion 444-435.
- Khan H, Belsler J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest*. 2007;131:1308-1314.
- Huber-Wagner S, Quick M, Mussack T, et al. Massive blood transfusion and outcome in 1062 polytrauma patients: a prospective study based on the Trauma Registry of the German Trauma Society. *Vox Sang*. 2007;92:69-78.
- Mitra B, Mori A, Cameron PA, et al. Massive blood transfusion and trauma resuscitation. *Injury*. 2007;38:1023-1029.
- Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma*. 2006;60(6 Suppl):S91-S96.
- 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.
- Kashuk JL, Moore EE, Sauaia A, et al. Postinjury life-threatening coagulopathy: is 1:1 the answer? *J Trauma*. 2008. In press.
- Maier RV, Banker P, McKinley B, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care [foreword]. *J Trauma*. 2005;59:762-763.
- Moore FA, McKinley BA, Moore EE, et al. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. III. Guidelines for shock resuscitation. *J Trauma*. 2006;61:82-89.
- Minei JP, Nathens AB, West M, et al. Inflammation and the Host response to injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. II. Guidelines for prevention, diagnosis and treatment of ventilator-associated pneumonia (VAP) in the trauma patient. *J Trauma*. 2006;60:1106-1113; discussion 1113.
- Nathens AB, Johnson JL, Minei JP, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. I. Guidelines for mechanical ventilation of the trauma patient. *J Trauma*. 2005;59:764-769.
- West MA, Shapiro MB, Nathens AB, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. IV. Guidelines for transfusion in the trauma patient. *J Trauma*. 2006;61:436-439.
- Harbrecht BG, Minei JP, Shapiro MB, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. VI. Blood glucose control in the critically ill trauma patient. *J Trauma*. 2007;63:703-708.
- Brandt CA, Deshpande AM, Lu C, et al. TrialDB: a web-based Clinical Study Data Management System. *AMIA Annu Symp Proc*. 2003;794.
- Carrico CJ, Meakins JL, Marshall JC, et al. Multiple-organ-failure syndrome. *Arch Surg*. 1986;121:196-208.
- Marshall JC. Organ dysfunction as an outcome measure in clinical trials. *Eur J Surg Suppl*. 1999;(584):62-67.
- Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995;23:1638-1652.
- Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995;38:185-193.
- Shackford SR, Mackersie RC, Holbrook TL, et al. The epidemiology of traumatic death. A population-based analysis. *Arch Surg*. 1993;128:571-575.
- 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.
- Holcomb JB. Damage control resuscitation. *J Trauma*. 2007;62(6 Suppl):S36-S37.
- Ketchum L, Hess JR, Hiippala S. Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. *J Trauma*. 2006;60(6 Suppl):S51-S58.
- Stanworth SJ, Brunskill SJ, Hyde CJ, et al. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol*. 2004;126:139-152.
- MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. *J Trauma*. 2006;60(6 Suppl):S46-S50.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.

Reprinted with permission from Journal of Trauma 2008; 65(5):986-93. Sperry JL, Ochoa JB, Gunn SR, et al. An FFP:PRBC transfusion ratio $\geq 1:1.5$ is associated with a lower risk of mortality after massive transfusion. Copyright © 2008 Wolters Kluwer Health, Lippincott Williams & Wilkins. <http://www.lww.com/>