ORIGINAL ARTICLE

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The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study

Comparative Effectiveness of a Time-Varying Treatment With Competing Risks

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Objective: To relate in-hospital mortality to early transfusion of plasma and/or platelets and to time-varying plasma:red blood cell (RBC) and platelet:RBC ratios.

Design: Prospective cohort study documenting the timing of transfusions during active resuscitation and patient outcomes. Data were analyzed using time-dependent proportional hazards models.

Setting: Ten US level I trauma centers.

Patients: Adult trauma patients surviving for 30 minutes after admission who received a transfusion of at least 1 unit of RBCs within 6 hours of admission (n=1245, the original study group) and at least 3 total units (of RBCs, plasma, or platelets) within 24 hours (n=905, the analysis group).

Main Outcome Measure: In-hospital mortality.

Results: Plasma:RBC and platelet:RBC ratios were not constant during the first 24 hours ($P<.001$ for both). In a multivariable time-dependent Cox model, increased ratios of plasma:RBCs (adjusted hazard ratio=0.31; 95% CI, 0.16-0.58) and platelets:RBCs (adjusted hazard ratio=0.55; 95% CI, 0.31-0.98) were independently associated with decreased 6-hour mortality, when hemorrhagic death predominated. In the first 6 hours, patients with ratios less than 1:2 were 3 to 4 times more likely to die than patients with ratios of 1:1 or higher. After 24 hours, plasma and platelet ratios were unassociated with mortality, when competing risks from nonhemorrhagic causes prevailed.

Conclusions: Higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received transfusions of at least 3 units of blood products during the first 24 hours after admission. Among survivors at 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios.

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INJURY IS INCREASING IN INCIdence, the second leading cause of death worldwide, and the leading cause of years of life lost in the United States.[1,2] Uncontrolled hemorrhage after injury is the leading cause of potentially preventable death.[3-9] As opposed to other major causes of traumatic death (eg, traumatic brain injury and multiple organ failure), hemorrhagic deaths occur quickly and are frequently associated with massive transfusion (MT) (traditionally defined as ≥10 units of red blood cells [RBCs] in 24 hours).[10,11] Current transfusion practices consist of infusing crystalloid, RBCs, plasma, and platelets and date back to the 1970s when separation of donated whole blood into its component parts became commonplace.[12-16]

A new resuscitation strategy, termed *damage control resuscitation*, is challenging the status quo.[17] The term originated in the US military and refers to the guidelines developed for combat casualties with substantial bleeding in Iraq and Afghanistan. Among other interventions, this approach recommends earlier and more balanced transfusion of plasma and platelets along with the first units of RBCs (ie, maintaining plasma:platelet:RBC ratios closer to the 1:1:1 ratio of whole blood) while simultaneously minimizing crystalloid use[18-27] in patients to avert or reverse the triad of coagulopathy, acidosis, and hypothermia[25,28-30] and decrease endothelial permeability.[31-33]

Conflicting findings regarding the association between transfusion ratios closer to 1:1 and survival in MT trauma pa-

tients have been reported[29,34-36] and attributed to multiple issues, including survival bias.[34,35,37,38] Survival bias, also known as reverse causation, is a prevalent, important, and often neglected problem in clinical observational studies, systematic reviews, and comparative effectiveness research.[39,40] In trauma resuscitation research, the conundrum of reverse causation is whether treatment caused patients to survive longer or patients received treatment only because they survived long enough. Without compelling evidence to guide uniform transfusion practice for trauma patients with substantial bleeding after injury, considerable variation persists across level I trauma centers.[14,19,41]

Using prospective, minute-to-minute observational data from 10 level I trauma centers, our objectives were to accurately describe when RBCs, plasma, and platelets were infused and to assess the association between in-hospital mortality and the timing and amount of blood products. One purpose of observational clinical studies is to inform the design of future randomized trials, and exploratory analysis can provide critical information regarding trial feasibility, realistic estimates of expected effect size, and unique insights from real-world health care settings. Thus, we describe the rationale, results, and lessons learned from our exploratory analyses of Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study data.[42] We hypothesized that early transfusion of plasma and platelets in higher ratios would be associated with decreased in-hospital mortality in bleeding patients.

METHODS

STUDY SAMPLES

The PROMMTT Study was a prospective, multicenter, observational cohort study conducted at 10 level I trauma centers in the United States. At each study site and the Data Coordinating Center, the local institutional review board approved the study. The US Army Human Research Protections Office provided a second-level review and approval.[42]

Trauma patients were enrolled in the PROMMTT Study and data collection was begun at emergency department arrival. Patients were eligible if they required the highest level of trauma activation, were aged 16 years or older, and received a transfusion of at least 1 unit of RBCs in the first 6 hours after admission. Patients were excluded if they met the following criteria: (1) were transferred from other facilities; (2) were declared dead within 30 minutes of admission; (3) had received more than 5 minutes of cardiopulmonary resuscitation prior to or within 30 minutes of admission; (4) were prisoners; (5) had a burn injury of more than 20% of the total body surface area; (6) had inhalation injury as diagnosed by bronchoscopy; or (7) were pregnant. If ineligibility was first identified sometime after enrollment, the patient was withdrawn from the study and postenrollment data were destroyed. No changes in clinical practice were implemented in this observational study. All participating centers had MT protocols in place.[42]

DATA COLLECTION AND MANAGEMENT

Standard operating procedure manuals were developed and site coordinators were trained in a series of meetings. Research assistants available at all hours screened and enrolled patients, recording the exact times of fluid infusion and blood product transfusion as well as patient outcomes during direct observation. Direct bedside observation began at trauma team activation and continued until active resuscitation ended (defined as the time the center transfusion protocol was discontinued, death occurred, or 2 hours elapsed since the last blood product transfusion, whichever came first). After direct observation ended, new interventions, complications, and outcomes were recorded daily while the patient was in the intensive care unit and weekly thereafter during hospitalization. Cause of in-hospital death was ascribed by individual site clinicians without confirmation or central adjudication. Sites of bleeding were ascertained by data collectors. The Data Coordinating Center audited study data for missing values and outliers.[42] Some severely injured patients did not undergo routine baseline assessments (eg, base deficit, temperature, international normalized ratio, pH) owing to the emergent nature of their injuries (**Table 1**).

STATISTICAL ANALYSIS

The primary outcome of interest was in-hospital mortality. In the original analysis plan, the primary independent variables were single plasma:RBC and platelet:RBC transfusion ratios.[42] Under the assumption that each patient would receive constant ratios of plasma and platelets during the period of active resuscitation, the PROMMTT Study was designed to enroll 1200 transfused and 300 MT patients. Previous retrospective studies suggested that higher plasma and platelet ratios occurred in about 25% to 50% of MT patients[19] and were associated with at least a 50% decrease in mortality relative to lower ratios.[19,23,43] Thus, at the $\alpha = .05$ significance level, a total of at least 300 PROMMTT Study MT patients was expected to provide 80% power[44] to detect differences of at least 50% in mortality between 2 groups of patients classified by transfusion ratios (ratios closer to 1:1 vs ratios closer to 1:2).

Previous retrospective trauma transfusion studies have focused on the subgroup of MT patients, effectively excluding bleeding patients who did not survive long enough to receive 10 RBC units and heightening the concern for survival bias.[19,37] Finding reliable and immediate indicators for patients' blood loss and continuing hemorrhage rates is a challenge in trauma transfusion practice and research.[45] Cumulative counts of patients' total RBC units received within 6 to 24 hours (especially to identify the MT subgroup) remain a standard, but poor, surrogate. Soon after the PROMMTT Study began, we realized the need to revise the original analysis plan to account for heterogeneity among patients (eg, variations in the severity of blood loss and rates of continuing hemorrhage) and trauma centers (eg, variations in blood product availability, MT protocols, and blood bank to bedside transit times).[34-37] We therefore sought an exploratory approach to analysis that would incorporate the requirements for time-dependent and multilevel techniques and thereby reduce the potential for bias.

To test the hypothesis that plasma:RBC and platelet:RBC ratios closer to 1:1 were independently and jointly associated with lower in-hospital mortality than transfusion ratios closer to 1:2, we reasoned that only PROMMTT Study patients surviving long enough to receive at least 3 blood product units (including 1 unit of RBCs) should be eligible to be included in the analysis. Patients who had received a transfusion of less than 3 units by hour 24 (or death) had no opportunity to attain 1:1 ratios for both plasma:RBCs and platelets:RBCs (ie, the same ratios as whole blood). Follow-up time at risk of death for each patient began at minute 31 or the start of the third unit transfused, whichever occurred last because eligible PROMMTT Study patients had to survive the first 30 minutes after admission and

Table 1. Admission and Treatment Characteristics and Unadjusted Survival in 1245 Prospective, Observational, Multicenter, Major Trauma Transfusion Study Patients

Characteristic	All Enrolled Patients (N = 1245)		Analysis Cohort (n = 905)	
	Median (IQR)	Nonmissing, No.	Median (IQR)	Nonmissing, No.
At admission				
Age, y	38 (24-54)	1244	37 (24-53)	904
Male, No. (%)	923 (74.2)	1245	687 (75.9)	905
Blunt injury, No. (%)	796 (64.5)	1235	579 (64.4)	899
Systolic blood pressure, mm Hg	106 (86-128)	1213	102 (82-124)	876
Heart rate, beats/min	105 (86-124)	1218	109 (88-128)	887
Temperature, °C	36.1 (35.6-36.6)	630	36.1 (35.6-36.6)	440
Glasgow Coma Scale	14 (3-15)	1135	13 (3-15)	826
Base deficit	6 (3-10)	960	7 (4-11)	716
pH	7.3 (7.2-7.3)	975	7.3 (7.2-7.3)	730
International normalized ratio	1.2 (1.1-1.4)	1081	1.3 (1.1-1.5)	792
Partial thromboplastin time, s	27 (24-33)	1045	29 (25-35)	762
Prothrombin time, s	15 (13-17)	902	15 (14-17)	662
Hemoglobin, g/dL	11.7 (10.1-13.3)	1198	11.5 (9.9-13.1)	869
Injury Severity Score	25 (16-34)	1243	26 (17-36)	905
Bleeding site, No. (%)[a]				
Head	181 (14.5)	1245	128 (14.1)	905
Face	340 (27.3)	1245	246 (27.2)	905
Neck	57 (4.6)	1245	41 (4.5)	905
Chest	299 (24.0)	1245	237 (26.2)	905
Abdomen	396 (31.8)	1245	320 (35.4)	905
Pelvis	164 (13.2)	1245	143 (15.8)	905
Limb	441 (35.4)	1245	334 (36.9)	905
Unknown	121 (9.7)	1245	79 (8.7)	905
At treatment				
Damage control surgery performed, No. (%)	239 (19.3)	1241	222 (24.6)	904
Time to first units transfused, min				
RBCs	30 (12-99)	1222	25 (11-77)	905
Plasma	69 (35-133)	815[b]	69 (35-130)	778[b]
Platelets	123 (81-190)	357[b]	121 (80-187)	343[b]
Total units				
At 6 h				
RBCs	4 (2-7)	1224	5 (3-9)	905
Plasma	2 (0-5)	1224	4 (2-7)	905
Platelets	0 (0-6)	1224	0 (0-6)	905
At 24 h				
RBCs	5 (2-9)	1244	6 (4-11)	905
Plasma	4 (0-8)	1245	5 (2-9)	905
Platelets	0 (0-6)	1245	0 (0-6)	905
Unadjusted in-hospital mortality, No. (%)				
30 min to 6 h	102 (8.2)	1245	95 (10.5)	905
>6 h to 24 h	46 (4.0)	1143	37 (4.6)	810
>24 h to 30 d	112 (10.2)	1097	88 (11.4)	773
Overall cumulative	266 (21.4)	1245	226 (25.0)	905

Abbreviations: IQR, interquartile range; RBCs, red blood cells.
SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.
[a] Bleeding site categories are not mutually exclusive and patients were counted in multiple categories if appropriate.
[b] Numbers exclude any patient who did not receive plasma or platelets during direct observation.

long enough to receive at least 3 blood product units. Cumulative ratios of plasma:RBCs and platelets:RBCs and summed counts of blood products transfused were computed at baseline (entry to follow-up) and for up to 14 consecutive time intervals: (1) two 15-minute intervals between minute 31 and hour 1; (2) ten 30-minute intervals between more than 1 and 6 hours; (3) one 18-hour interval between more than 6 and 24 hours; and (4) one 29-day interval between more than 24 hours and 30 days. The timing of transfusion was defined by the time of initiation of each transfusion. Cell-saver transfusions were not enumerated or combined with donor blood products in these analyses.

We first examined whether transfusion ratios among PROMMTT Study patients in the analysis cohort were constant across time by using mixed linear regression models for both continuous plasma:RBC and platelet:RBC ratios. We then performed multilevel time-dependent Cox proportional hazards regression that uses time as a continuous variable to accommodate the following: (1) varying entry times for this dynamic analysis cohort; (2) time-varying cumulative sums of transfusion, plasma:RBC ratios, and platelet:RBC ratios; (3) important patient baseline covariates; and (4) any residual variation in mortality rates due to unmeasured center influences. Center random effects were assessed using shared frailty, which

Table 2. Distribution of Reported Cause of Death for Decedent Patients in the Analysis Cohort by the Time Period of Death[a]

Cause of Death, No. (%)[b]	Patients Dying Within the Interval, No. (%)							
	>0.5 to ≤1 h (n = 8)	>1 to ≤3 h (n = 55)	>3 to ≤6 h (n = 32)	>6 to ≤12 h (n = 21)	>12 to ≤24 h (n = 16)	>24 to ≤72 h (n = 21)	>72 h to ≤30 d (n = 67)	>30 d (n = 6)
Hemorrhage	7 (88)	46 (84)	24 (75)	9 (43)	3 (19)	3 (14)	3 (4)	0
Brain injury	0	9 (16)	10 (31)	10 (48)	10 (63)	13 (62)	32 (48)	1 (17)
Airway/respiratory	1 (13)	2 (4)	3 (9)	2 (10)	1 (6)	2 (10)	15 (22)	3 (50)
Sepsis	0	0	0	0	0	1 (5)	6 (9)	2 (33)
Multiple organ failure	0	0	0	0	0	2 (10)	24 (36)	5 (83)
Cardiovascular	4 (50)	16 (29)	6 (19)	4 (19)	3 (19)	3 (14)	6 (9)	2 (33)
Other	0	5 (9)	4 (13)	2 (10)	3 (19)	1 (5)	18 (27)	1 (17)

[a] Column percentages sum to greater than 100% because patients may have more than 1 contributing cause of death.
[b] Not centrally adjudicated.

assumed a single hazard factor (eg, unmeasured clinical practices) for each trauma center shared by all of its patients. Hazard ratios (as an estimate of standard relative risk), 95% CIs, and *P* values were estimated.

Similar to previous retrospective studies of the association between transfusion ratios and in-hospital mortality among trauma patients,[19] our initial time-dependent Cox analysis spanned the entire follow-up period of 30 days, and a separate analysis focused on the first 24 hours after emergency department admission. The proportional hazards assumption was tested using Schoenfeld residuals for each covariate and the global test proposed by Grambsch et al.[46] Results from these tests suggested significant violations of the assumptions underlying the Cox models for both the full 30-day period (global test, $P < .001$) and the first 24 hours of follow-up (global test, $P < .001$), so subsequent analyses are presented in 3 intervals (30 minutes to 6 hours, >6 hours to 24 hours, and >24 hours to 30 days). In the models stratified by these time intervals, the proportional hazards assumptions were not violated (global test, $P = .13$, .48, and .40, respectively). Because transfusions were generally completed by 6 hours, only the proportional hazards model for the first interval (30 minutes to 6 hours) included time-dependent covariates.

We applied purposeful variable selection strategies[47] that retained in all models the plasma and platelet ratios as the primary independent variables of interest and the sum of transfusions, age, time interval at cohort entry, and Injury Severity Score as the primary potential confounders of interest. The remaining covariates of head, chest, and limb bleeding sites were retained in all models because they were significant at the $\alpha = .05$ level and changed the magnitude of the plasma or platelet ratio coefficients by more than 20% when compared with models excluding them for 1 or more of the separate time intervals examined. The other candidate covariates listed in Table 1 did not change the magnitude of the plasma or platelet ratio coefficients by more than 20% and were not significant when compared with models excluding them; they were therefore not retained in the final models.[48] No interactions (each transfusion ratio multiplied by the alternative ratio or a primary covariate) were significant at the $\alpha = .05$ level. The transfusion ratios were also modeled categorically using clinically relevant cut points. The lowest ratios (<1:2) defined the reference group; ratios of 1:2 or higher and of less than 1:1 defined the moderate group; and ratios of 1:1 or higher defined the high group. Patients discharged in less than 30 days were censored alive at 30 days.

All analyses were performed using SAS/STAT version 9.2 statistical software for Windows (SAS Institute, Inc) and Stata/MP version 11 statistical software (StataCorp LP). Manuscript preparation was guided by the Strengthening the Reporting of Observational Studies in Epidemiology statement for the reporting of cohort studies in epidemiology[49] and the Standards for Quality Improvement Reporting Excellence standards for the reporting of improvement studies in health care.[50]

RESULTS

There were 34 362 trauma admissions in the 10 centers over an average of 58 weeks. Data collection was initiated for 12 560 patients; of these, 11 315 became ineligible and were withdrawn from the study and 1245 met all PROMMTT Study eligibility criteria. Of these, 905 received a transfusion of 3 or more units of blood products, thus meeting the eligibility criteria for the analysis cohort (eFigure, http://www.archsurg.com). Overall in-hospital mortality was 21% for all 1245 transfused patients and 25% for patients included in the analysis cohort (Table 1).

Among cohort patients, 94% of hemorrhagic deaths occurred within 24 hours, the majority of these deaths (60%) occurred within 3 hours of admission (**Table 2**), and the median time to hemorrhagic death was 2.6 hours (interquartile range, 1.7-5.4 hours). The principal causes of in-hospital death after 24 hours were multiple organ failure and brain injury.

Neither plasma:RBC nor platelet:RBC ratios were constant across the first 24 hours among individual patients (**Figure 1**) ($P < .001$ for each patient in the analysis cohort). The time-varying nature of plasma and platelet transfusion practice across the analysis cohort is illustrated in **Figure 2**. Thirty minutes after admission, 67% of cohort patients had not received plasma, while 99% had not received platelets. Three hours after admission (the peak time of hemorrhagic death), 10% of surviving cohort patients had not received any plasma, while 28% of survivors had not received platelets. For each successive hour survived (up to hour 6), patients were more likely to receive plasma and platelets and hence were more likely to approach ratios of 1:1. By 30 minutes, 1 hour, 2 hours, 3 hours, and 6 hours after admission, ratios exceeded 1:2 in 29%, 47%, 69%, 78%, and 84% of surviving cohort patients for plasma and in 1%, 14%, 40%, 60%, and 80% for platelets, respectively.

The protective association between higher transfusion ratios and mortality in the first time interval (minute 31 to hour 6) diminished during the next 2 time intervals

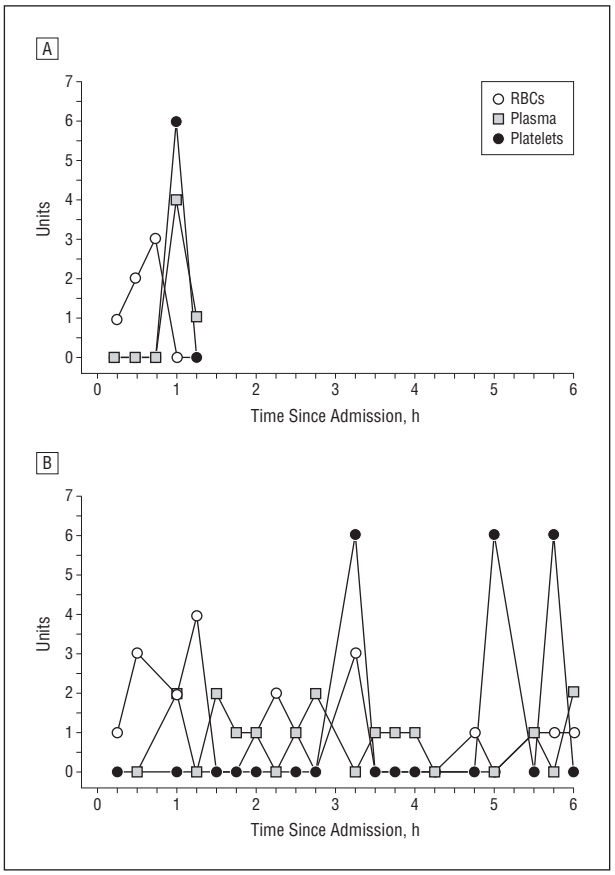

Figure 1. Blood product use in the first 6 hours in 2 Prospective, Observational, Multicenter, Major Trauma Transfusion Study patients. Patient 1 (A) had an Injury Severity Score of 48 and died of hemorrhage at 1 hour 7 minutes after emergency department admission. Patient 2 (B) had an Injury Severity Score of 57 and was discharged to another acute care hospital at 27 days. Note the constantly changing ratios over time. For example, patient 1 received cumulative plasma:platelet:red blood cell (RBC) ratios of 0:0:1, 0:0:3, 0:0:6, 4:6:6, and 5:6:6 at 15, 30, 45, 60, and 75 minutes, respectively, while patient 2 received cumulative plasma:platelet:RBC ratios of 0:0:1, 0:0:4, 0:0:4, 2:0:6, and 2:0:10 at those same times.

(**Table 3**). The trend for plasma ratios suggested that the decreased mortality risk observed during the first 6 hours (adjusted hazard ratio = 0.31; $P = <.001$) switched direction and became nonsignificant by the final follow-up period of more than 24 hours to 30 days (adjusted hazard ratio = 1.21; $P = .20$). The association between the platelet:RBC ratio and mortality remained below the null but was not significant for either of the later periods. Additionally, bleeding from the chest was associated with higher mortality during the first 6 hours; in contrast, among patients who survived longer than 6 hours, bleeding from the chest was associated with lower mortality.

To facilitate clinical use, we repeated the same Cox models but substituted patients' continuous transfusion ratio values with 3 categorical ones (Table 3). In the initial 6-hour interval, patients in the moderate- and high-ratio groups had lower mortality rates than the low-ratio group ($P < .001$ for each of the higher plasma ratio groups; $P = .04$ for the high platelet ratio group). In both subsequent intervals, mortality among survivors was not associated with the categorical ratios.

COMMENT

In-hospital mortality among 1245 trauma patients receiving at least a single unit of RBCs within 6 hours of admission was 21% (Table 1), while cohort patients with 3 or more units transfused had in-hospital mortality of 25%, among the highest of any acute surgical disease process. The major findings were that patients did not receive a constant ratio during the period of active resuscitation and that early infusion of higher plasma and platelet ratios was associated with decreased mortality within 6 hours of admission, during which 81% of the hemorrhagic deaths had occurred (Table 2).

The protective association between higher transfusion ratios and in-hospital mortality appears strongest within 6 hours and diminishes over time as the primary

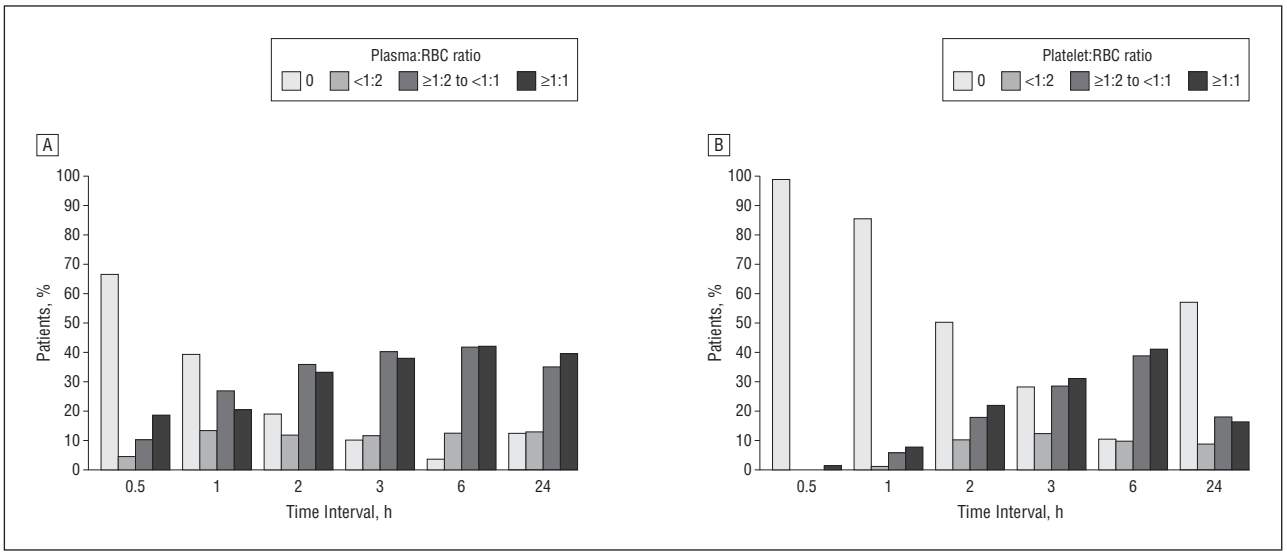

Figure 2. The bars represent cumulative ratios at the start of each time interval. Most patients received a plasma:red blood cell (RBC) ratio of 1:2 or higher by 3 hours (A) and a platelet:RBC ratio of 1:2 or higher by 6 hours (B). In the last time interval (24 hours), the percentage of patients receiving 0 units of platelets or plasma increases, reflecting the dynamic cohort with newly eligible patients entering and others exiting owing to death in the previous interval.

Table 3. Multivariable Cox Regression Models Examining the Association of Plasma and Platelet Transfusion Ratios With In-hospital Mortality

Characteristic	Continuous Transfusion Ratio Variables		Categorical Transfusion Ratio Variables				
			Low, <1:2	Moderate, ≥1:2 to <1:1		High, ≥1:1	
	HR (95% CI)	*P* Value	HR	HR	*P* Value	HR	*P* Value
Minute 31 to Hour 6 After ED Admission (n = 876)[a]							
Early initial and time-varying plasma:RBC ratios	0.31 (0.16-0.58)	<.001	1 [Reference]	0.42	<.001	0.23	<.001
Early initial and time-varying platelet:RBC ratios	0.55 (0.31-0.98)	.04	1 [Reference]	0.66	.16	0.37	.04
Sum of blood product transfusions	1.05 (1.04-1.06)	<.001	[b]				
Age	1.01 (1.00-1.02)	.03					
Injury Severity Score	1.02 (1.01-1.04)	.001					
Time interval at cohort entry	0.73 (0.63-0.86)	<.001					
Bleeding from head	3.73 (2.15-6.45)	<.001					
Bleeding from chest	1.52 (0.96-2.39)	.07					
Bleeding from limb	0.54 (0.32-0.89)	.02					
Hour >6 to Hour 24 After ED Admission (n = 809)[c]							
6-h cumulative plasma:RBC ratio	0.34 (0.14-0.81)	.02	1 [Reference]	0.79	.63	0.55	.23
6-h cumulative platelet:RBC ratio	0.81 (0.46-1.43)	.46	1 [Reference]	0.79	.56	0.49	.19
Sum of blood product transfusions at hour 6	1.04 (1.03-1.05)	<.001	[b]				
Age	1.01 (0.99-1.03)	.36					
Injury Severity Score	1.02 (0.99-1.04)	.11					
Time interval at cohort entry	0.84 (0.72-0.98)	.03					
Bleeding from head	8.46 (3.82-18.7)	<.001					
Bleeding from chest	0.87 (0.39-1.97)	.74					
Bleeding from limb	0.96 (0.48-1.92)	.90					
Hour >24 to Day 30 After ED Admission (n = 773)[d]							
24-h cumulative plasma:RBC ratio	1.21 (0.90-1.61)	.20	1 [Reference]	1.41	.33	1.47	.26
24-h cumulative platelet:RBC ratio	0.78 (0.57-1.06)	.11	1 [Reference]	1.23	.46	0.69	.19
Sum of blood product transfusions at hour 24	1.02 (1.01-1.03)	<.001	[b]				
Age	1.03 (1.02-1.04)	<.001					
Injury Severity Score	1.04 (1.02-1.05)	<.001					
Time interval at cohort entry	0.98 (0.91-1.06)	.63					
Bleeding from head	5.96 (3.59-9.90)	<.001					
Bleeding from chest	0.45 (0.23-0.90)	.02					
Bleeding from limb	1.22 (0.76-1.96)	.41					

Abbreviations: ED, emergency department; HR, hazard ratio; RBC, red blood cell.

[a] Time-dependent Cox model examining the association of plasma and platelet ratios with mortality within 6 hours of ED admission, adjusted for the sum of blood product transfusions (also time varying), baseline covariates, and center random effects. Of 904 patients with complete data who entered the cohort over 24 hours, 876 entered the cohort during this initial interval and 94 died within the 5.5 hours of follow-up.

[b] Covariate HRs are not repeated because differences were negligible comparing the models with categorical vs continuous transfusion ratios.

[c] Regular Cox model examining the association of cumulative plasma and platelet ratios with mortality between more than 6 to 24 hours after ED admission, adjusted for baseline covariates and center random effects. Of 809 patients surviving the initial 6 hours, 27 patients entered the cohort in the second interval and 37 died within the next 18 hours of follow-up.

[d] Regular Cox model examining the association of cumulative plasma and platelet ratios with mortality between more than 24 hours to 30 days after ED admission, adjusted for baseline covariates and center as a fixed effect (the model did not converge with site as a random effect). Of 773 patients surviving 24 hours, 1 patient entered the cohort in the third interval and 88 died within the next 29 days of follow-up.

causes of mortality shift from exsanguination to head injury, respiratory distress, organ failure, and infection after the first 24 hours. These time trends reflect heterogeneity as the dynamic cohort of injured patients changes during the course of hospitalization in composition and risk profile owing to mortality. Survivors avoiding early hemorrhage-related mortality face the longer-term competing risks of death from complications (eg, multiple organ failure) or multiple injuries (eg, head injury). The significant protective association between higher blood product ratios and mortality that we observed was concentrated in the first 24 hours for plasma and the first 6 hours for platelets. Thereafter, during the later time periods of high competing risks for nonhemorrhagic causes of death among severely injured patients, plasma and platelet ratios were not significantly associated with mortality.

Survival bias may have threatened previous studies that used (1) the traditional definition of MT and therefore excluded patients who had substantial bleeding but died early[19,29,34,35,51]; (2) a single cumulative ratio for plasma or platelets up to the time of death or 6 to 24 hours after admission and therefore did not account for time-dependent treatment[19,23,29,35,36,52-55]; and (3) 30-day or overall in-hospital mortality as the primary end point, which conflates competing mortality risks.[19,23,28,29,34-36,51-56] Our prospective study design, detailed real-time data collection methods, and analysis strategies attempted to minimize the effect of survival bias.

In rapidly and substantially bleeding trauma patients, inadequate transfusion of plasma and platelets is associated with early death. However, the actual transfusion of blood products is a complicated balance be-

tween rapid recognition of need, ordering of appropriate products, product availability in the blood bank and emergency department, obtaining those products quickly, and appropriate infusion. Unless these steps are orchestrated in an integrated fashion, delayed infusion and suboptimal ratios will occur (Figure 1 and Figure 2). Clinicians must rapidly identify patients who are substantially bleeding, and several predictive algorithms have been developed to do this.[57-67]

Once bleeding patients have been identified, constant ratios are not infused and heterogeneous transfusion practice persists (Figure 2). Clinicians at PROMMTT level I trauma centers ultimately delivered plasma ratios of 1:1 and 1:2 within 6 to 24 hours to surviving patients. However, platelet infusion lagged behind with only 72% of patients receiving platelets by hour 3, the median time to hemorrhagic death.

Stratifying by time interval and including time-dependent covariates (Table 3) revealed how early infusion and increased ratios were associated with decreased mortality (30 minutes to 6 hours). However, it is difficult to translate hazard ratios for continuous variables into a physician's order to the blood bank for the delivery of specific blood product amounts. Therefore, we created 3 clinically relevant categories and found that a 1:1 ratio of plasma and platelets was associated with decreased early mortality compared with lower ratios (Table 3).

The strengths of this study are its prospective multicenter design and teaming a dedicated Data Coordinating Center (epidemiologists, informatics experts, and biostatisticians) with a group of level I trauma centers. By identifying patients who received at least 3 units of blood products instead of focusing on MT patients, we reduced one important source of survival bias. Accurate recording of the actual timing of blood product transfusions combined with appropriate data analysis strategies addressed another source of survival bias, ie, the time-varying nature of blood transfusions and mortality. Limitations of our observational study include missing values on potentially important covariates, which are unavoidable in observational studies of severely injured trauma patients, and other unmeasured but potentially important confounders and effect modifiers (eg, the time of and rationale for physicians' orders for RBCs, plasma, and platelets). Survival was not ascertained after discharge; however, deaths within days of discharge from an acute care hospital are infrequent (<2%).[68] Finally, causes of death were assigned by individual site clinicians without confirmation or central adjudication.

In summary, these prospective data suggest that the association between earlier and higher ratios of plasma and platelets and decreased in-hospital mortality is concentrated in the first 6 hours in patients with substantial bleeding. In the first 6 hours, patients with ratios lower than 1:2 were 3 to 4 times more likely to die than patients with ratios of 1:1 or higher. Among survivors at 6 hours, the subsequent risk of death by hour 24 was higher for patients with low plasma ratios. Among survivors at 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios. Furthermore, these data highlight the serious problems of survival bias and competing risks in most previous trauma resuscitation studies[37,56] and emphasize the need for definitive comparative effectiveness trauma transfusion research.

Survival bias can be eliminated only in a randomized trial with appropriate design and analysis strategies. However, it can threaten even a randomized trial if study patients are stratified by postrandomization events such as the conventional MT definition. This study supports a potential net survival benefit of early and higher plasma and platelet ratios to be assessed in a randomized trial.[69] Our findings offer guidance and evidence for designing a rigorous, multicenter, randomized transfusion trial by identifying the following: (1) transfusion ratios in common use at level I trauma centers; (2) well-defined end points (eg, 3, 6, and 24 hours and 30-day mortality); (3) appropriate data analysis strategies accounting for time-varying covariates; (4) effect size estimates for power and sample size considerations; (5) patients for whom interventions should be targeted; and (6) procedures that promote integrated, consistent transfusion practices across individual clinicians, blood banks, research teams, and trauma centers.

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