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Staying on target: Maintaining a balanced resuscitation during damage-control resuscitation improves survival

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BACKGROUND: Damage-control resuscitation (DCR) improves survival in severely bleeding patients. However, deviating from balanced transfusion ratios during a resuscitation may limit this benefit. We hypothesized that maintaining a balanced resuscitation during DCR is independently associated with improved survival.

METHODS: This was a secondary analysis of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study. Patients receiving >3 U of packed red blood cells (PRBCs) during any 1-hour period over the first 6 hours and surviving beyond 30 minutes were included. Linear regression assessed the effect of percent time in a high-ratio range on 24-hour survival. We identified an optimal ratio and percent of time above the target ratio threshold by Youden's index. We compared patients with a 6-hour ratio above the target and above the percent time threshold (on-target) with all others (off-target). Kaplan-Meier analysis assessed the combined effect of blood product ratio and percent time over the target ratio on 24-hour and 30-day survival. Multivariable logistic regression identified factors independently associated with 24-hour and 30-day survival.

RESULTS: Of 1,245 PROMMTT patients, 524 met the inclusion criteria. Optimal targets were plasma/PRBC and platelet/PRBC of 0.75 (3:4) and ≥40% time spent over this threshold. For plasma/PRBC, on-target (n = 213) versus off-target (n = 311) patients were younger (median, 31 years; interquartile range, [22–50] vs. 40 [25–54]; $p = 0.002$) with similar injury burdens and presenting physiology. Similar patterns were observed for platelet/PRBC on-target (n = 116) and off-target (n = 408) patients. After adjusting for differences, on-target plasma/PRBC patients had significantly improved 24-hour (odds ratio, 2.25; 95% confidence interval, 1.20–4.23) and 30-day (odds ratio, 1.97; 95% confidence interval, 1.14–3.41) survival, while on-target platelet/PRBC patients did not.

CONCLUSION: Maintaining a high ratio of plasma/PRBC during DCR is independently associated with improved survival. Performance improvement efforts and prospective studies should capture time spent in a high-ratio range. (*J Trauma Acute Care Surg.* 2021;91: 841–848.

LEVEL OF EVIDENCE: Epidemiologic/prognostic study, level II; Therapeutic, level IV.

KEY WORDS: Coagulopathy; PROMMTT; massive transfusion; shock; hemorrhagic; resuscitation.

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Trauma deaths in the United States total an estimated 200,000 annually,[1,2] and of these, approximately 50,000 are from acute hemorrhage.[3] Recent analysis suggests that many of these deaths are potentially preventable;[4–8] nearly 20,000 in-hospital trauma deaths per year could be eliminated by providing optimal clinical care to these critically injured bleeding patients.[1] To reduce potentially preventable death from trauma, the most common cause of death, hemorrhage, requires improved therapeutic approaches.[5–9]

Recent advances in early hemorrhage control and resuscitation have directly addressed this vexing problem.[3,10] The use of massive transfusion protocols (MTPs) supporting the practice of damage-control resuscitation (DCR) is associated with improved survival in severely injured trauma patients.[11] The landmark Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study demonstrated improved 6-hour survival if ratios of plasma and platelet to packed red blood cell (PRBC) transfusion were closer to 1:1 as compared with less than 1:2.[12] The subsequent Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study did not demonstrate improved overall 24-hour mortality but did show that 1:1:1 plasma to platelets to PRBC transfusion decreased early death from exsanguination.[13]

However, global acceptance of and adherence to DCR principles remains surprisingly low. A survey of US trauma centers participating in the Trauma Quality Improvement Project indicated that up to 16% continue to use a resuscitation strategy that prioritizes PRBCs over plasma or platelets.[14] The PROMMTT study also demonstrated significant practice variations among participating trauma centers with regard to blood product ratios during the course of a resuscitation. However, the effect of these practice variations resulting in wide swings in blood product ratios, often well below the hemostatic target, remains unknown. We hypothesized that maintaining a balanced resuscitation throughout DCR is independently associated with improved survival.

PATIENTS AND METHODS

This study was approved with a waiver of informed consent by the University of Pennsylvania Investigational Review Board. The investigators adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects).

Patients and Data Collection

This was a secondary analysis of the PROMMTT study.[12] The design of the PROMMTT study has been described in detail elsewhere.[15] Briefly, this prospective observational study was conducted at 10 level I US trauma centers from July 2009 to October 2010. All 10 participating trauma centers had preexisting MTPs in place but demonstrated substantial variations in transfusion practice.[15] Study subjects included patients who were at least 16 years of age, required the highest-level trauma activation, and received at least 1 U of PRBCs within the first 6 hours of admission. Patients were excluded if they were transferred from another facility, pronounced dead within 30 minutes of arrival, had more than 5 minutes of cardiopulmonary resuscitation before or within the first 30 minutes of admission, had burns of greater than 20% total body surface area, were diagnosed with inhalation injury, were prisoners, or were pregnant.

Resuscitation data were collected prospectively starting at 30 minutes following trauma center arrival (t_{30}), at 15-minute intervals for two additional time points (t_{45} and t_{60}), and then at 30-minute intervals thereafter by independent research assistants who were staffed 24/7. Resuscitation data collection continued until death, transfusion protocol discontinuation, or 2 hours after blood product transfusion for up to 6 hours. Study data audits assured complete and accurate records of each resuscitation.[15]

For this secondary analysis, we included massive transfusion (MT) patients who received more than 3 U of PRBCs within any 1-hour interval during the first 6 hours, which we termed critical administration threshold positive (CAT+).[16] We also assessed alternative definitions of MT including the traditional 10 U or more of PRBC in 24 hours[17] and resuscitation intensity.[18] Our primary endpoint was 24-hour survival, and 30-day survival was a secondary endpoint.

Analytical Variables and Definitions

Blood product ratios for plasma to PRBC (plasma/PRBC) and platelets to PRBC (platelet/PRBC) were defined as the cumulative ratio at 6 hours or at the end of data collection, whichever came first. Optimal 6-hour ratios for plasma/PRBC and platelet/PRBC were then identified based on 24-hour survival using Youden's index, max(sensitivity + specificity − 1). We also assessed optimal 6-hour ratios for 30-day survival.

We then evaluated the effect of time spent above and below these optimal blood product ratios. First, we performed linear regression analysis to assess the relationship between time over the optimal ratio and 24-hour survival. We then determined the percent time spent over the optimal ratio for both plasma/PRBC and platelet/PRBC for each patient. Percent time was calculated as the number of minutes spent above the optimal threshold divided by the total resuscitation time. Total resuscitation time was defined as 6 hours for survivors or the time of death for nonsurvivors (Supplemental Fig. 1, http://links.lww.com/TA/C3). We performed sensitivity analysis on alternative definitions for the percent time to include only time to hemostasis or only the first 2 hours of resuscitation since the majority of patients achieved hemostasis by 105 minutes.[13]

From the optimal ratio and the optimal percent time spent above this ratio, each patient's DCR profile was then categorized as either on-target (6-hour ratio ≥ optimal target and percent time ≥ optimal target) and off-target (all others) for both plasma and platelets to PRBCs. Unadjusted Kaplan-Meier survival analysis was performed on the patient cohorts. Significant differences between patients who survived and those who died were identified, and multivariable logistic regression was performed to determine factors independently associated with 24-hour and 30-day survival.

Patient cohorts were assessed using descriptive statistics. Categorical variables were compared using the χ^2 test, and continuous variables were evaluated using the Wilcoxon-Mann-Whitney test. Statistical significance was defined as $p < 0.05$. Power analysis indicated that 96 patients per cohort would be required to achieve 0.8 power for 24-hour survival. All analyses were performed using SAS Enterprise version 9.4 (Cary, NC). Article preparation was guided by the STROBE statement for the reporting of cohort studies in epidemiology (checklist provided as Supplemental Digital Content, http://links.lww.com/TA/C2).

RESULTS

Of 1,245 patients in the PROMMTT study, we identified 524 CAT+ patients who comprised our study cohort (Supplemental Fig. 2, http://links.lww.com/TA/C3; Supplemental Table 1, http://links.lww.com/TA/C3). Of the CAT+ patients, 78% were male, the median age was 37 years, and 37% had a penetrating injury (Table 1). Of note, there was no difference in outcome based on injury mechanism on unadjusted analysis. In addition, 408 (77.9%) survived 24 hours, and 355 (67.7%) survived 30 days (Table 2). Exsanguination was the most prevalent overall cause of death at 24 hours and 30 days. On-target plasma/PRBC patients had a lower rate of death from exsanguination compared with off-target patients at both 24 hours (10.3% vs. 20.6%, $p = 0.003$) and 30 days (11.7% vs. 20.6%, $p = 0.011$). Similarly, fewer on-target platelet/PRBC died from exsanguination at 24 hours (7.8% vs. 18.9%, $p = 0.007$) and 30 days (8.6% vs. 19.4%, $p = 0.010$) (Supplemental Table 2, http://links.lww.com/TA/C3).

TABLE 1. Baseline Demographics Comparison for CAT+ Cohort

		Plasma/PRBC			Platelet/PRBC		
	CAT+	Off-target	On-target		Off-target	On-target	
	(n = 524)	(n = 311)	(n = 213)	*p*	(n = 408)	(n = 116)	*p*
Age, y	37 (24–52)	40 (25–54)	31 (22–50)	0.002	36 (23–52)	43 (24–55)	0.064
Men	408 (77.9)	245 (78.8)	163 (76.5)	0.615	323 (79.2)	85 (73.3)	0.222
Penetrating	191 (36.5)	106 (34.1)	85 (39.9)	0.205	148 (36.3)	43 (37.1)	1.000
Blunt	326 (62.2)	199 (62.0)	127 (59.6)	0.358	255 (62.5)	71 (61.2)	0.885
Other	7 (1.3)	6 (1.9)	1 (0.5)	0.297	5 (1.2)	2 (1.7)	1.000
ISS	29 (17–41)	27 (17–41)	29 (19–38)	0.320	29 (17–38)	29 (18–42)	0.420
AIS head	0 (0–3)	0 (0–3)	0 (0–3)	0.464	0 (0–3)	0 (0–4)	0.013
AIS chest	3 (0–4)	3 (0–4)	3 (0–4)	0.436	3 (0–4)	3 (0–3)	0.020
AIS abdomen	2 (0–4)	2 (0–4)	3 (0–4)	0.508	2 (0–4)	2 (0–4)	0.820
Systolic BP, mm Hg	98 (80–122)	99 (78–123)	98 (80–120)	0.925	99 (80–122)	98 (81–123)	0.507
HR, beats per minute	111 (89–132)	110 (89–132)	112 (89–131)	0.644	113 (96–98)	105 (86–123)	0.097
Temperature, °C	35.0 (35.6–36.6)	36.1 (35.4–36.5)	36.1 (35.6–36.7)	0.353	36.1 (35.6–36.6)	35.9 (35.6–36.3)	0.126
GCS	5 (3–15)	6 (3–15)	3 (3–15)	0.661	7 (3–15)	3 (3–14)	0.022
pH	7.2 (7.1–7.3)	7.2 (7.1–7.3)	7.2 (7.1–7.3)	0.637	7.2 (7.1–7.3)	7.3 (7.1–7.3)	0.008
Base deficit	1.0 (0.5–3.8)	0.6 (0.3–5.0)	1.0 (1.0–2.6)	0.855	1.0 (0.2–2.9)	2.5 (0.9–4.9)	0.452
Lactate, mg/dL	5.2 (3.3–8.8)	5.3 (3.5–8.1)	5.1 (3.3–9.2)	0.864	5.3 (3.2–8.3)	5.1 (3.7–8.9)	0.983
Hemoglobin, g/dL	11.1 (9.4–12.7)	11.1 (9.6–12.7)	11.2 (9.3–12.8)	0.940	11.4 (9.9–12.8)	10.1 (8.8–12.0)	0.001
PTT, s	30.4 (25.2–38.8)	28.0 (24.8–35.6)	32.5 (26.5–41.8)	<0.001	30.1 (25.1–36.7)	33.0 (26.4–41.0)	0.072
PT, s	15.9 (14.1–18.7)	15.0 (12.8–17.7)	17.3 (15.1–19.9)	<0.001	15.6 (14.0–18.4)	17.4 (14.7–21.2)	0.004
INR	1.3 (1.2–1.6)	1.2 (1.1–1.5)	1.4 (1.2–1.7)	<0.001	1.3 (1.2–1.6)	1.4 (1.2–1.7)	0.032
OR intervention	424 (80.9)	254 (81.7)	170 (79.8)	0.675	331 (81.1)	93 (80.2)	0.923

All values are presented as n (%) or median (IQR).
CAT+, patients requiring more than 3 U of PRBCs within any hour during the first 6 hours.
On-target, patients with a 6-hour ratio >0.75 and who spent ≥40% of their time above this threshold.
Off-target, all other patients not meeting on-target criteria.
BP, blood pressure; GCS, Glasgow Coma Scale; HR, heart rate; INR, international normalized ratio; IQR, interquartile range; ISS, Injury Severity Score; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 2. Comparison of Transfusion Requirements and Mortality for CAT+ Cohort

		Plasma/PRBC			Platelet/PRBC		
	CAT+	Off-target	On-target		Off-target	On-target	
	(n = 524)	(n = 311)	(n = 213)	*p*	(n = 408)	(n = 116)	*p*
6-h Plasma/PRBC	0.72 (0.47–0.96)	0.50 (0.33–0.67)	1.00 (0.86–1.04)	<0.001	0.67 (0.40–0.90)	0.87 (0.67–1.00)	<0.001
6-h Platelet/PRBC	0.29 (0.00–0.80)	0.00 (0.00–0.73)	0.54 (0.00–0.86)	<0.001	0.00 (0.00–0.50)	1.03 (0.86–1.33)	<0.001
6-h Plasma	6 (3–11)	4 (2–8)	8 (6–14)	<0.001	5 (3–10)	8 (4–13)	0.001
6-h Platelet	6 (0–12)	0 (0–6)	6 (0–12)	0.002	0 (0–6)	12 (6–18)	<0.001
6-h PRBC	8 (5–15)	8 (5–16)	8 (5–14)	0.668	8 (5–15)	8 (6–14)	0.697
24-h Plasma/PRBC	0.75 (0.50–1.00)	0.52 (0.33–0.70)	1.00 (0.86–1.22)	<0.001	0.69 (0.44–0.94)	0.83 (0.67–1.10)	<0.001
24-h Platelet/PRBC	0.40 (0.00–0.75)	0.23 (0.00–0.73)	0.55 (0.00–0.86)	<0.001	0.00 (0.00–0.55)	1.00 (0.75–1.24)	<0.001
24-h Plasma	7 (4–14)	5 (2–11)	10 (6–16)	0.504	7 (4–14)	9 (5–16)	0.013
24-h Platelet	6 (0–12)	3 (0–12)	6 (0–12)	<0.001	0 (0–11)	12 (6–18)	<0.001
24-h PRBC	10 (6–18)	9 (6–19)	10 (6–16)	<0.001	10 (6–19)	9 (6–16)	0.851
Died in 3 h	57 (10.9)	49 (15.8)	8 (3.8)	<0.001	54 (13.2)	3 (2.6)	0.002
Died in 6 h	87 (16.6)	68 (21.9)	19 (8.9)	<0.001	79 (19.4)	8 (6.9)	0.002
Died in 24 h	116 (22.1)	83 (26.7)	33 (15.5)	0.003	103 (25.2)	13 (11.2)	0.002
Died in 30 d	169 (32.3)	113 (36.3)	56 (26.3)	0.020	137 (33.6)	32 (27.6)	0.269

All values are n (%) or median (IQR).
CAT+, patients requiring more than 3 U of PRBCs within any hour during the first 6 hours.
On-target, patients with a 6-hour ratio >0.75 and who spent ≥40% of their time above this threshold.
Off-target, all other patients not meeting on-target criteria.
IQR, interquartile range.

Youden's index analysis identified the optimal 6-hour plasma/PRBC ratio of 0.77 (95% confidence interval [CI], 0.74–0.80) and the optimal platelet/PRBC ratio of 0.75 (95% CI, 0.70–0.80) (Supplemental Fig. 3, http://links.lww.com/TA/C3). This methodology was repeated for 30-day survival (Supplemental Tables 3 and 4, http://links.lww.com/TA/C3). From these results, a pragmatic optimal ratio of 0.75 (3:4) plasma/PRBC and platelet/PRBC was used for all subsequent analyses. Patients with a 6-hour plasma/PRBC ratio ≥ the optimal ratio had a 24-hour survival of 82.6% versus 73.4% (p = 0.012), while patients who had a 6-hour platelet/PRBC ratio ≥ the optimal ratio had a 24-hour survival of 86.2% versus 74.5% (p = 0.003).

Linear regression assessing the effect of percent time (minutes) over the optimal ratio of 0.75 on predicted survival demonstrated improved 24-hour survival with increased time over this ratio for both plasma/PRBC (p = 0.010) and platelet/PRBC (p = 0.011) (Fig. 1). Youden's index was then used to determine an optimal percent of time over the target ratio. This demonstrated an optimal threshold of 42% resuscitation time spent over the optimal target ratio for both plasma/PRBC and platelet/PRBC (Supplemental Tables 3 and 4, http://links.lww.com/TA/C3). A pragmatic 40% time threshold was selected for both plasma/PRBC and platelet/PRBC for subsequent analyses. On sensitivity analysis, using alternative time exposure intervals for calculating the optimal percent time above a target ratio of 0.75 did not improve model performance; however, using the time exposure interval of "time to hemostasis" effectively differentiated 24-hour survivors from nonsurvivors (Supplemental Table 5, http://links.lww.com/TA/C3).

Based on cumulative 6-hour plasma/PRBC ratio and percent time over this optimal ratio, 213 (40.6%) were classified as on-target, while 311 (59.4%) were classified as off-target. On-target plasma/PRBC patients had a 24-hour survival of 83.3% (177 of 213 patients) as compared with 73.3% (228 of 311 patients) for off-target patients (p = 0.003) (Table 2, Fig. 2*A*). Similarly, for platelet/PRBC, 116 (22.1%) were classified as on-target, while 408 (77.8%) were classified as off-target. On-target platelet/PRBC patients had a 24-hour survival of 88.8% (103 of 116 patients) compared with 74.8% (305 of 408 patients) for off-target patients (p = 0.002) (Table 2, Fig. 2*B*). Unadjusted survival analysis demonstrated early separation of the survival curves for these patients with significantly greater survival in the on-target group for both plasma/PRBC (p = 0.001 by log rank) and platelet/PRBC (p = 0.001 by log rank) (Fig. 3).

In comparing patients who survived to those who died, we included Injury Severity Score, Abbreviated Injury Scale (AIS)

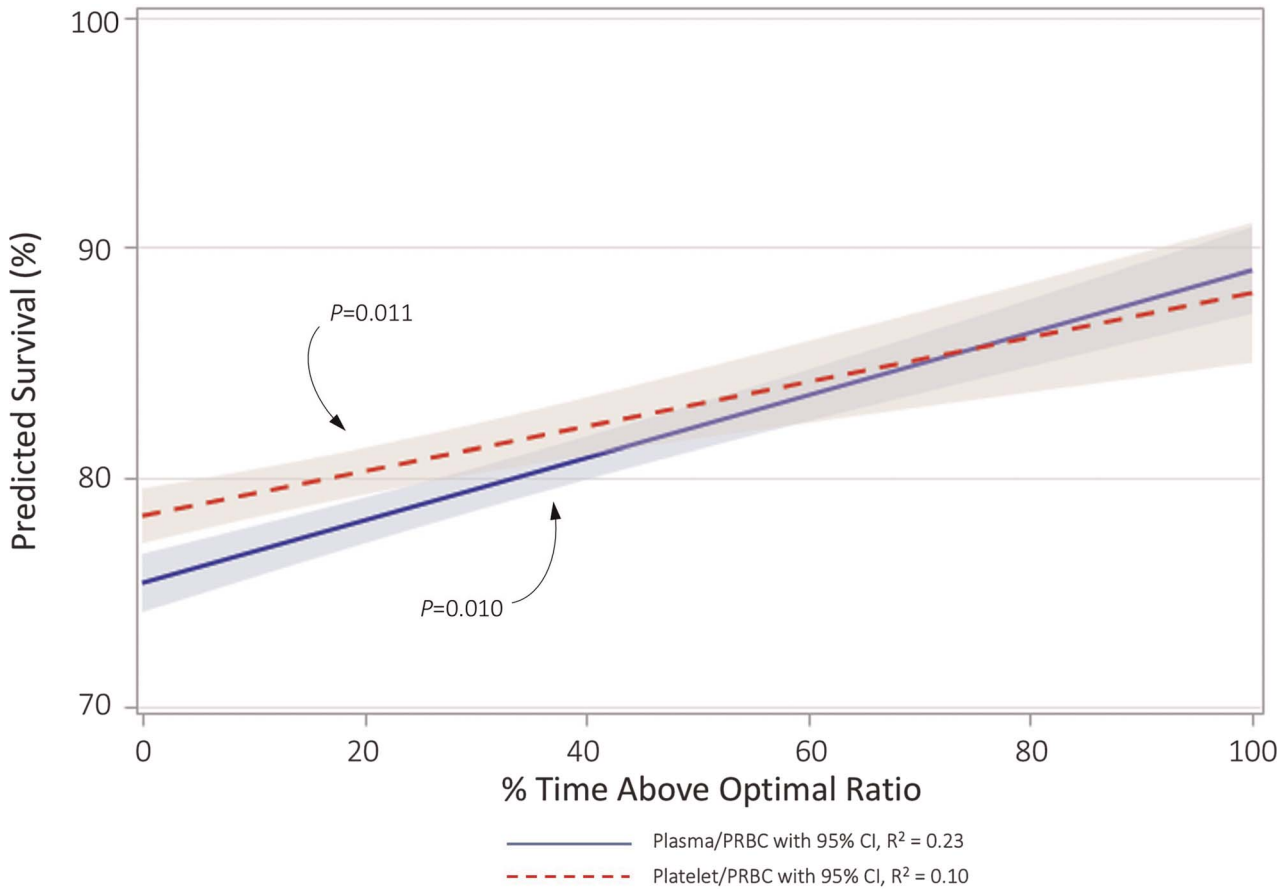

Figure 1. Linear regression showing predicted survival (%) as a function of percent time spent at or above the optimal ratio of 0.75 (3:4) for both plasma/PRBC and platelet/PRBC.

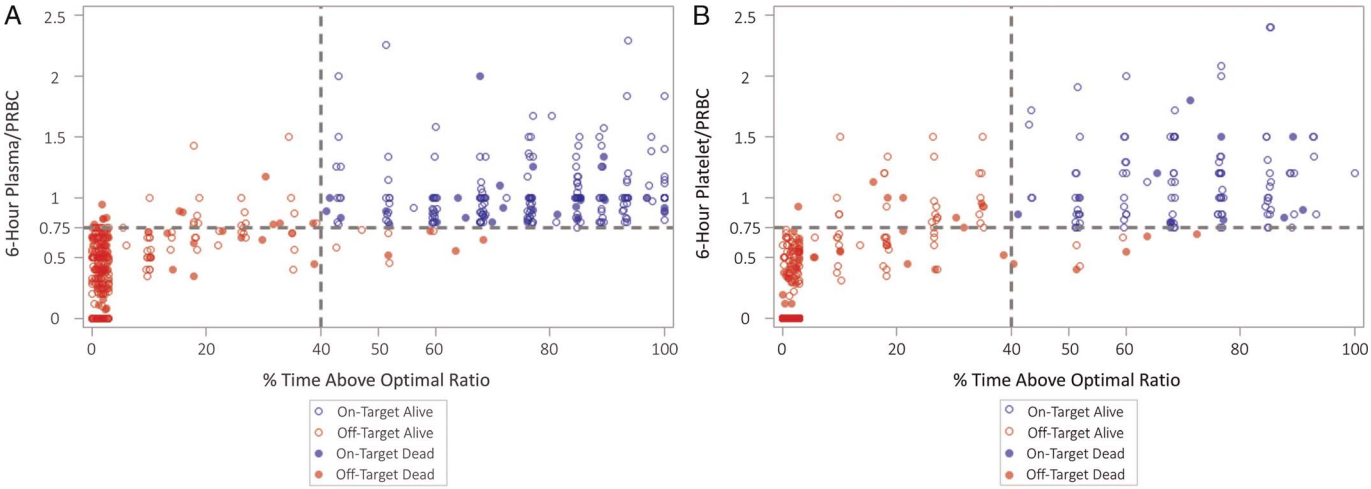

Figure 2. Scatter plot of 6-hour blood product ratio and percent time spent at or above the optimal ratio of 0.75 (3:4) divided into On-Target (blue) and Off-Target (red) cohorts. Overplotting was avoided by a 2% noise reduction through jittering the graph. (*A*), Plasma/PRBC. (*B*), Platelet/PRBC.

chest, heart rate, prothrombin time, on-target plasma/PRBC, and on-target platelet/PRBC as covariates in our final model for 24-hour survival. For 30-day survival, we included age, AIS head, admission hemoglobin, prothrombin time, on-target plasma/PRBC and on-target platelet/PRBC. This demonstrated an independent survival benefit for on-target plasma/PRBC at 24 hours (odds ratio [OR], 2.25; 95% CI, 1.20–4.23; $p = 0.012$) and 30 days (OR, 1.97; 95% CI, 1.14–3.41; $p = 0.015$) (Fig. 4). However, no such independent association was identified for on-target platelet/PRBC. Increased time spent above the optimal plasma/PRBC ratio by 30-minute intervals (OR, 1.16; 95% CI, 1.07–1.25; $p < 0.001$), 1-hour intervals (OR, 1.34; 95% CI, 1.14–1.57; $p < 0.001$), and 3-hour intervals (OR, 2.38; 95% CI, 1.48–3.82; $p < 0.001$) was also independently associated with improved 24-hour survival. However, a similar independent association was not demonstrated for increased 30-minute intervals (OR, 1.10; 95% CI, 0.98–1.23; $p < 0.108$), 1-hour intervals (OR, 1.20; 95% CI, 0.96–1.51; $p < 0.108$), or 3-hour intervals (OR, 1.75; 95% CI, 0.89–3.44; $p < 0.108$) above a high platelet/PRBC ratio.

DISCUSSION

In this secondary analysis of PROMMTT, we sought to determine whether maintaining a balanced resuscitation throughout DCR is associated with improved survival in severely injured patients at risk for death from hemorrhage. This study demonstrates that early empiric resuscitation should target a high ratio of both plasma and platelets to PRBC (≥0.75) and that this high resuscitation ratio needs to be maintained throughout the resuscitation to optimize survival. In particular, maintaining this high ratio of plasma to PRBC for at least 40% of the patient's initial 6 hours of resuscitation was independently associated with improved 24-hour and 30-day survival and a lower frequency of cause of death from exsanguination at 24 hours and 30 days. Furthermore, every 30-minute increment in maintaining this

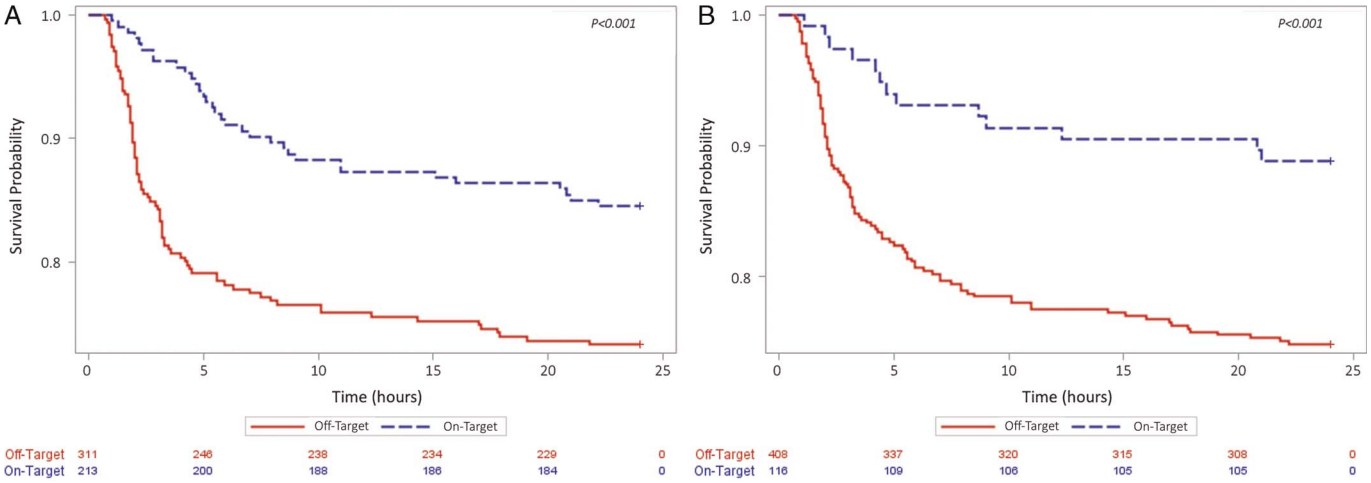

Figure 3. Kaplan-Meier 24-hour survival analysis on the On-Target (blue) and Off-Target (red) cohorts. (*A*), Plasma/PRBC. (*B*), Platelet/PRBC.

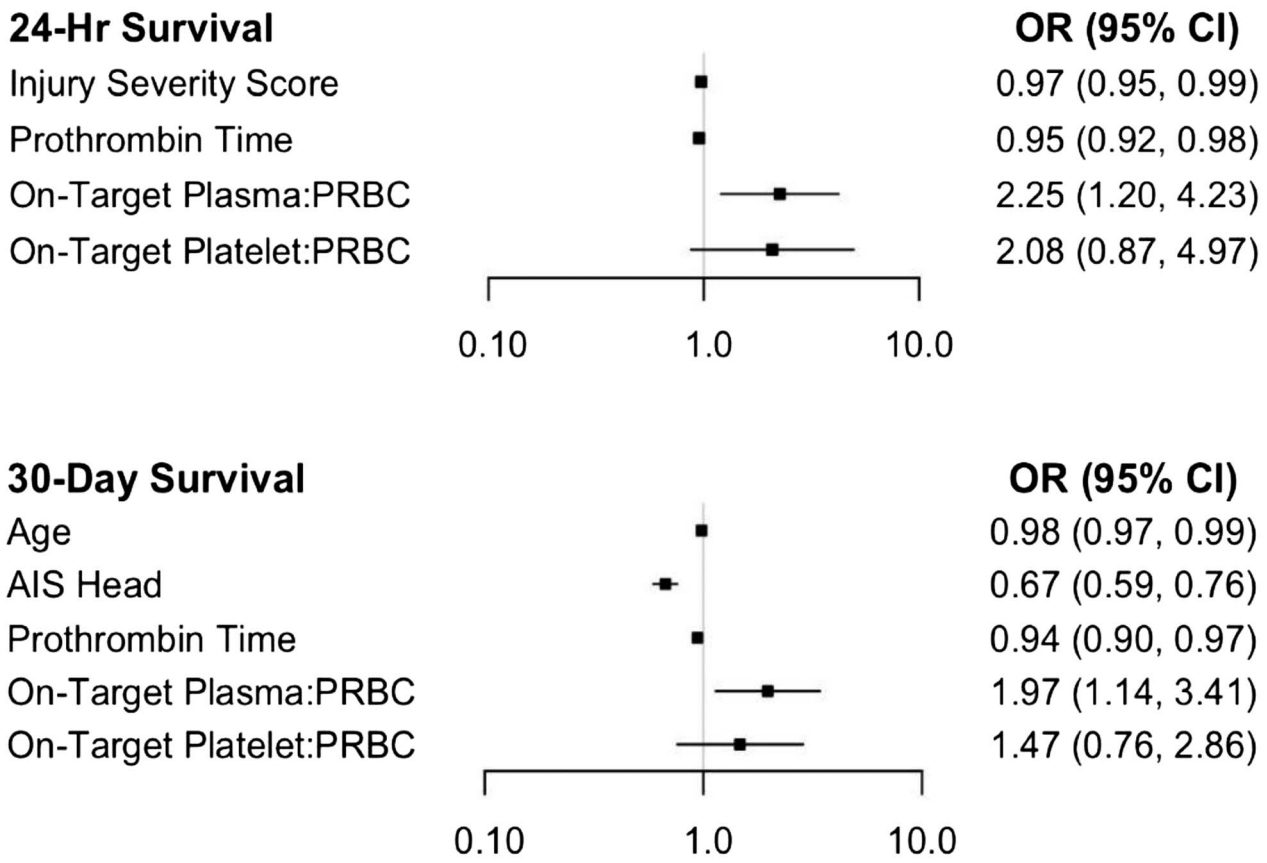

Figure 4. Multivariable logistic regression model assessing survival at 24 hours and 30 days.

high ratio was independently associated with improved survival. Although unadjusted analysis indicated an association between maintaining a high ratio of platelet to PRBC, this association did not persist on adjusted analysis.

The concept of DCR has transformed trauma resuscitation practice over the past three decades by emphasizing a number of concepts including minimizing crystalloid-based resuscitation, optimizing transfusion ratios, and administering hemostatic adjuncts.[19–23] Despite this evolution, hemorrhage remains the leading cause of preventable death from trauma.[9,24,25] This prompted us to consider the potential role of dynamic component ratios on survival and whether belatedly "catching up" to a balanced ratio could compromise some of the benefit seen with DCR.

To study this effect, we sought to identify a subpopulation within the PROMMTT study truly at risk for death from exsanguination. Traditionally, the MT population meets these criteria; however, the historic metric of receiving ≥10 U of PRBC within 24 hours introduces survivor bias. Recently, Savage et al. defined MT by rate and volume termed CAT+: any patient who received at least 3 U of PRBC in any 1 hour over the course of 24 hours.[16,26] This definition mitigates the survival bias that occurs when early death precludes the patient from receiving 10 U of PRBCs. In our analysis, we used a modified form of the CAT definition of more than 3 U during the index 6 hours as opposed to the 24 hours used in the traditional CAT definition since the average time to hemostasis in the PROMMTT study was 105 minutes.[13]

After selecting these CAT+ patients who were actively exsanguinating, like others, we sought to derive an optimal blood product ratio.[11,13,17,27–31] In our analysis, the optimal plasma/PRBC ratio of 0.75 is consistent with previous studies.[17,27,32–34] In addition, our 0.75 optimal platelet/PRBC ratio was consistent with a high ratio of 0.66 previously analyzed by Brown et al.[32] and Holcomb et al.[33] It is possible, however, that the optimal platelet/PRBC ratio may indeed be higher than 0.75.[29,35,36]

Although there has been much attention on cumulative blood product ratios, very little work to date has focused on how blood product ratios over time impacts survival.[11] Recent studies have indicated an important element of timeliness in DCR, though.[37] Meyer et al.[38] used the PROPPR data set to demonstrate the association between every minute delay in the activation and arrival of the first blood cooler and mortality. Regardless of the ratio, there was a 5% increase in the odds of mortality for every minute transfusion was delayed. In our study, we evaluated the effect of both the cumulative ratio (≥0.75 or <0.75) and the duration of maintaining that ratio (≥40% or <40% resuscitation time) on survival. Ultimately, a 6-hour plasma/PRBC of at least 0.75 for at least 40% of the resuscitation time was independently associated with improved 24-hour and 30-day survival. Furthermore, for every 30 minutes, 1 hour, and 3 hours over this ratio, 24-hour survival was also improved.

The strength of this study is that these results were obtained from the prospective multicenter PROMMTT study conducted at 10 level 1 trauma centers that met rigorous selection criteria for study participation. Nonetheless, our secondary analysis of this study contains several important limitations. First, confounding variables unmeasured in this study included resuscitation adjuncts such as calcium,[39] tranexamic acid,[40] recombinant factor VIIa,[41] fibrinogen,[42] prothrombin complex concentrate,[43] and vasopressin.[44] Crystalloid was considered; however, it did not reach statistical significance. Second, relatively few patients received platelets, and the various MTPs used by participating PROMMTT sites provided platelets later in the resuscitation.[12] In the original study, only 343 (38%) of study patients received platelets, and the first platelet transfusion was given at a median of 121 minutes (interquartile range, 80–187 minutes). As a result, our adjusted analysis on time-in-target for platelets/PRBCs may have been underpowered to detect a clinically meaningful survival difference with optimal platelet transfusion. Nonetheless, we were able to calculate an optimal platelet/PRBC ratio for 24-hour mortality adjusted for age, sex, systolic blood pressure, heart rate, Glasgow Coma Scale score, international normalized ratio, AIS head, AIS chest. Finally, Youden's index may not be the ideal approach to determining an optimal blood product ratio since it weighs sensitivity and specificity equally. In evaluating MTPs and DCR, it may be better to optimize sensitivity to maximize survival. In addition, some literature has suggested that there may be a U-shape curve surrounding the optimal ratio.[45,46] Youden's index further limits our ability to assess for such relationship.

Prospective Observational Multicenter Major Trauma Transfusion initially showed a protective association with mortality and higher transfusions during the index 24 hours. Expanding on the initial 24 hours, our secondary analysis indicated a protective association when considering both the optimal ratio and time above that ratio at both 24 hours and at 30 days. Regarding the generalizability of these results, some may note that this study included a large proportion of patients with penetrating injuries and that all participating level I trauma centers had preexisting MTPs. Both observations are true; however, we do not believe that they limit the generalizability of our findings. The pragmatic nature of the PROMMTT study actually captured important practice variations in resuscitation that enhanced the richness of this data set.[15] This feature of the data allowed us to identify a clearly superior resuscitation strategy that should prove effective for any patient with hemorrhagic shock and trauma-induced coagulopathy regardless of the original traumatic mechanism.

While PROPPR and PROMMTT were prospective trials analyzing transfusion ratios, there remains a paucity of prospective data regarding the impact of maintaining the optimal transfusion ratios.[12,13] We believe that future DCR studies and performance improvement efforts should include prospectively collected resuscitation signatures. This signature would assess not only how quickly the team recognizes and responds to an exsanguinating patient but also how well they adhere to DCR principles throughout the resuscitation. Through the assessment of how well the team stays on-target, future damage-control metrics can be created and used as benchmarks in performance improvement efforts such as the American College of Surgery Trauma Quality Improvement Guidelines.

CONCLUSION

In this secondary analysis of the prospective observational PROMMTT study, we found that maintaining a high ratio of plasma/PRBC during DCR is independently associated with improved survival at 24 hours and 30 days. Performance improvement reviews and future prospective studies should capture time spent in a high-ratio range.

AUTHORSHIP

A.M.H., Z.G., C.L.M., B.S.A., S.H., P.Z.C., C.E.W., and J.W.C. designed the study. A.M.H., Z.G., D.S., D.R.S., and J.W.C. searched the literature. Z.G., E.E.F., C.E.W., and J.W.C. collected the data. A.M.H., Z.G., E.E.F., C.L.M., D.N.H., A.J.Y., C.E.W., and J.W.C. analyzed the data. A.M.H., Z.G., D.S., E.F., C.L.M., D.R.S., D.N.H., B.S.A., A.J.Y., S.H., P.Z.C., C.E.W., and J.W.C. participated in data interpretation. A.M.H., Z.G., D.R.S., and J.W.C. drafted the article, which all authors critically revised and approved.

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The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision unless so designated by other documentation.

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