Maintaining a whole blood-centered transfusion improves survival in hemorrhagic resuscitation

Griffin J. Feinberg, ScM, Anastasia C. Tillman, MD, Marcelo L. Paiva, MPP, Brent Emigh, MD, Stephanie N. Lueckel, MD, ScM, FACS, Allyson M. Hynes, MD, FAAEM, FACEP, *and* **Tareq Kheirbek, MD, ScM, FACS**, *Providence, Rhode Island*

BACKGROUND: Whole blood (WB) transfusion has been shown to improve mortality in trauma resuscitation. The optimal ratio of packed red blood cells (pRBC) to WB in emergent transfusion has not been determined. We hypothesized that a low pRBC/WB transfusion ratio is associated with improved survival in trauma patients.

METHODS: We analyzed the 2021 Trauma Quality Improvement Program (TQIP) database to identify patients who underwent emergent surgery for hemorrhage control and were transfused within 4 hours of hospital arrival, excluding transfers or deaths in the emergency department. We stratified patients based on pRBC/WB ratios. The primary outcome was mortality at 24 hours. Logistic regression was performed to estimate odds of mortality among ratio groups compared with WB alone, adjusting for injury severity, time to intervention, and demographics.

RESULTS: Our cohort included 17,562 patients; of those, 13,678 patients had only pRBC transfused and were excluded. Fresh frozen plasma/pRBC ratio was balanced in all groups. Among those who received WB (n = 3,884), there was a significant increase in 24-hour mortality with higher pRBC/WB ratios (WB alone 5.2%, 1:1 10.9%, 2:1 11.8%, 3:1 14.9%, 4:1 20.9%, 5:1 34.1%, $p = 0.0001$). Using empirical cutpoint estimation, we identified a 3:1 ratio or less as an optimal cutoff point. Adjusted odds ratios of 24-hour mortality for 4:1 and 5:1 groups were 2.85 (95% confidence interval [CI], 1.19–6.81) and 2.89 (95% CI, 1.29–6.49), respectively. Adjusted hazard ratios of 24-hour mortality were 2.83 (95% CI, 1.18–6.77) for 3:1 ratio, 3.67 (95% CI, 1.57–8.57) for 4:1 ratio, and 1.97 (95% CI, 0.91–4.23) for 5:1 ratio.

CONCLUSION: Our analysis shows that higher pRBC/WB ratios at 4 hours diminished survival benefits of WB in trauma resuscitation. Further efforts should emphasize this relationship to optimize trauma resuscitation protocols. (*J Trauma Acute Care Surg.* 2024;96: 749–756.

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Whole blood; balanced resuscitation; hemorrhage control.

Resuscitation strategies of bleeding trauma patients have evolved throughout the years. Military and civilian experiences and studies have repeatedly demonstrated that resuscitation with blood products is superior to fluid-based resuscitation. This holds especially true when balanced component therapy (CT) is achieved and maintained (1:1:1 ratio of plasma, platelets, and packed red blood cells [pRBCs]).[1–4] However, high-volume resuscitation with imbalanced blood product transfusion may worsen trauma-induced coagulopathy, which significantly increases the risk of morbidity and mortality in trauma patients.[5–7] Therefore, balanced blood transfusion early in the management of patients with hemorrhagic injuries is considered the standard of care.

Because of technical, immunological, and logistical considerations, whole blood (WB) donations are routinely separated into their components instead of being wholly transfused.[8] However, experience with WB transfusion in the battlefield has resurrected its potential application in civilian trauma.[9–12] Recent examinations of WB in civilian trauma resuscitation have demonstrated a decrease in total transfusion volume while offering a superior hemostatic profile and comparable risks of hemolytic reactions to CT.[9,11–13] Further, WB has shown an added benefit in reducing both short-term and long-term mortalities as well as in-hospital complications in trauma resuscitation.[13–16]

This mortality benefit has led many trauma centers to use WB as the first blood product in trauma resuscitation transfusions before continuing with CT when massive transfusion protocol (MTP) is required.[17] Despite the increasing adaptation of WB, the number of studies examining its effectiveness[15,18] and safety[12] in mixed transfusion scenarios (WB and CT) remains relatively limited. The findings reported by these previous studies have demonstrated mixed results on mortality and the risk of adverse outcomes when comparing mixed WB transfusions with CT alone.[14–16,19] More recent studies have compared CT alone to WB added to traditional resuscitation protocols in a categorical approach, not accounting for volumes of transfused products.

Submitted: August 22, 2023, Revised: November 12, 2023, Accepted: November 16, 2023, Published online: December 21, 2023.

From the Department of surgery (G.J.F., A.C.T., M.L.P., B.E., S.N.L., T.K.), Brown University, Alpert School of Medicine, Providence, Rhode Island; Department of Emergency Medicine (A.M.H.), and Department of Surgery (A.M.H.), University of New Mexico School of Medicine, Albuquerque, New Mexico.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for correspondence: Tareq Kheirbek, MD, FACS, Brown University, Alpert School of Medicine, Trauma, Acute Care Surgery & Surgical Critical Care, Rhode Island Hospital, 593 Eddy Street, APC 435, Providence, RI 02903; email: tareq_kheirbek@brown.edu.

DOI: 10.1097/TA.0000000000004222

Carefully examining these studies, we identified two gaps that remain unanswered; there was no direct comparison between WB alone and CT alone, and there was generally no assessment of ideal transfused WB volume, especially in relation to the volume of subsequent CT transfusions. Thus, it is plausible that the added benefit of the limited early WB transfusion is eventually "diluted" with subsequent massive CT resuscitation.[17]

In this study, we aim to investigate the impact of different ratios of mixed blood resuscitations that utilize WB on the outcomes of injured patients requiring hemorrhage control interventions. We hypothesized that a low pRBC/WB transfusion ratio is associated with improved survival in trauma patients.

METHODS

This is a retrospective analysis of the 2021 Trauma Quality Improvement Program (TQIP) database. We aimed to evaluate adult trauma patients (>18 years old) who underwent hemorrhage control surgery at participating trauma centers and were transfused within 4 hours of hospital arrival with either WB, pRBC, or both. Hemorrhage control surgery in TQIP was defined as undergoing any of the following procedures for the purpose of controlling bleeding: laparotomy, thoracotomy, sternotomy, extremity procedures including management of mangled extremity, neck exploration, extraperitoneal pelvic packing, or other skin and soft tissue procedures. After constructing the study concept, we obtained 2021 TQIP data from the American College of Surgeons, being the most recently published data at the time of the analysis. Our aim was to determine the association of pRBC/WB ratio with mortality at 24 hours. Patients were excluded if they were transferred from another facility, died in the emergency department (ED), or only received pRBC. Since TQIP provides publicly available, unidentified pooled data, the study was exempt from full IRB review. Results are presented in accordance with The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Supplemental Digital Content 1, http://links.lww.com/TA/D437).

Our comparison groups were the different ratios of packed red blood to whole blood cell units administered during the first 4 hours of resuscitation (pRBC/WB). Beginning in 2021, TQIP began reporting transfusion volumes in milliliters (mL). This information was limited to the first 4 hours only. These were collected from trauma flow sheets, anesthesia records, operative reports, nursing flow charts, and blood bank records per the National Trauma Data Standards (NTDS). These volumes were converted to units per standard guidelines (1 unit of WB = 500 mL, 1 unit of pRBC = 350 mL, 1 unit of fresh frozen plasma (FFP) = 250 mL, and 1 unit of platelets = 300 mL).[20] Ratio of pRBC/WB was then categorized into five categories (1:1, 2:1, 3:1, 4:1, 5:1), in which each category includes ratios up to the next category and 5:1 indicates any ratio that was equal or higher than 5:1. Our primary outcome was mortality at 24 hours. Secondary outcomes included overall in-hospital mortality and reported in-hospital complications including acute respiratory distress syndrome, acute kidney injury, severe sepsis, deep vein thrombosis, unplanned intensive care unit stay, unplanned intubation, pneumonia, decubitus ulcer development, and unplanned return to the operating room. Patients who died in the first 24 hours were excluded from the in-hospital complications analyses to avoid survival bias effect. One exception was for unplanned return to the operating room as this could have occurred any time during the hospital stay. Unplanned return to the operating room excluded staged operation following damage-control surgery.

Analyses were adjusted for demographics (age, gender), injury severity and pattern (injury severity score, penetrating trauma), time to hemorrhage control surgery, hemodynamic status on presentation defined by shock index, Glasgow Coma Scale on presentation, total units of transfusion administered, and type of hemorrhage control surgery performed. Time to hemorrhage control surgery indicated time between presentation and surgical incision per NTDS. Total units transfused was calculated as the sum of WB, pRBC, and FFP units. Specific organ injuries were defined per ICD10-CM codes. To adjust for injury severity as well as anatomical location of injury the New Injury Severity Score (NISS) was included in the adjusted models. New Injury Severity Score is calculated similar to Injury Severity Score but uses the three most injured organs regardless of the body region. This was calculated using the ICDPIC-R package based on ICD10-CM codes. It was computed in R statistical software, then imported to STATA to complete the analysis.

Descriptive data are presented as frequencies for categorical variables, means for parametric continuous variables, and medians for nonparametric continuous variables. We applied Pearson's χ^2 test with Fisher's exact test for sparse values to test independence for categorical data. Parametric continuous data were compared between the different ratio groups using Wilks' Lambda test for equality. Nonparametric data were analyzed using Kruskal Wallis equality-of-population rank test. In-group comparisons were performed using Dunn's test with adjustment for multiple computations (Supplemental Material 1, http://links.lww.com/TA/D438). Trends in mortality rates per each increase in ratio group were compared using Cuzick's trend analysis. Multiple logistic regression analysis was performed to obtain adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for 24-hour mortality. We chose statistically significant and clinically important variables to include in the multiple logistic regression analysis. We tested the variables linearity using Box-Tidwell regression. This identified age and time to hemorrhage control surgery to not be linear. Therefore, age was categorized into three categories (18–45, 46–65, 66 and older). We also performed a log transformation of time to hemorrhage control surgery to correct nonlinearity in the model. Only 15 patients had time to hemorrhage control surgery recorded as 0 minutes, and they were excluded from the logistic regression analysis after log transformation. Model goodness-of-fit was tested using the Hosmer-Lemeshow test. Resulting predicted mortality was calculated and plotted in Figure 2. Empirical cutpoint estimation was performed using Liu method to estimate optimal cutoff point. Multivariable adjusted logistic regression analysis was then repeated while changing the reference value to different ratio groups in order to obtain in-group estimates. We then performed survival analysis to account for difference in time to death within the first 24 hours. We applied an adjusted Cox regression analysis to estimate hazard ratios of 24-hour mortality among the different groups, adjusting for the same variables that were used in the multiple logistic regression model. Significance was set at $p = 0.05$. We computed the analyses using a commercial statistical software (STATA/SE 17; StataCorp 2021, College Station, TX).

RESULTS

We identified 17,562 patients who underwent hemorrhage control surgery after accounting for inclusion and exclusion criteria. Of those, 13,678 patients received resuscitation with component therapy only, and therefore, were excluded from the final analytic cohort.

Our analytic cohort included 3,884 patients who received WB, either alone or in combination with pRBC (Fig. 1). On average, patients received 2 units of WB (interquartile range [IQR], 1–3) and 5 units of pRBC (IQR: 2–11). Aside from WB administration, transfusion of FFP was balanced (median FFP/pRBC ratio of 1:1) in all categories. Details regarding patients' demographics, injury patterns, and hemorrhage control procedures are listed in Table 1.

Mortality at 24 hours increased with increasing pRBC/WB ratio from 5.2% in the WB-only group, 10.9% in the 1:1 group, and up to 34.1% in the 5:1 or more group ($p = 0.0001$ using both χ^2 test and Cusick trend test) (Fig. 2). Within-group comparisons showed that both 4:1 and 5:1 ratios had a significantly higher mortality compared with WB alone ($p = 0.009$ and 0.008, respectively). Table 2 details the differences in incidence of mortality and in-hospital complications between the groups.

Multiple logistic regression analysis adjusting for demographics, injury severity, location and pattern, hemodynamic status, time to hemorrhage control surgery, type of hemorrhage control procedure, mental status, and total units of blood transfusions showed a significantly higher OR of 24-hour mortality in both the 4:1 group (OR, 2.85; 95% CI, 1.19–6.81) and the 5:1 group (OR, 2.89; 95% CI, 1.29–6.49) compared with WB only group. Hosmer-Lemeshow test indicated a good fit of the model ($\chi^2 = 8.90$, $p = 0.35$). Using Liu method of empirical cutpoint estimation, we identified ratio 3:1 or less as an optimal cutoff point for survival. Survival analysis using Cox regression showed higher hazard ratios in the 3:1, 4:1, and 5:1 transfusion ratio groups. Table 2 details adjusted OR and HR of 24-hour mortality for each of the ratio groups with WB considered the reference group. Full results of the regression models, as well as summary of the in-group estimates of mortality are presented in the Supplemental Materials, http://links.lww.com/TA/D438. Figure 3 shows Kaplan-Meier survival curves up to 24 hours.

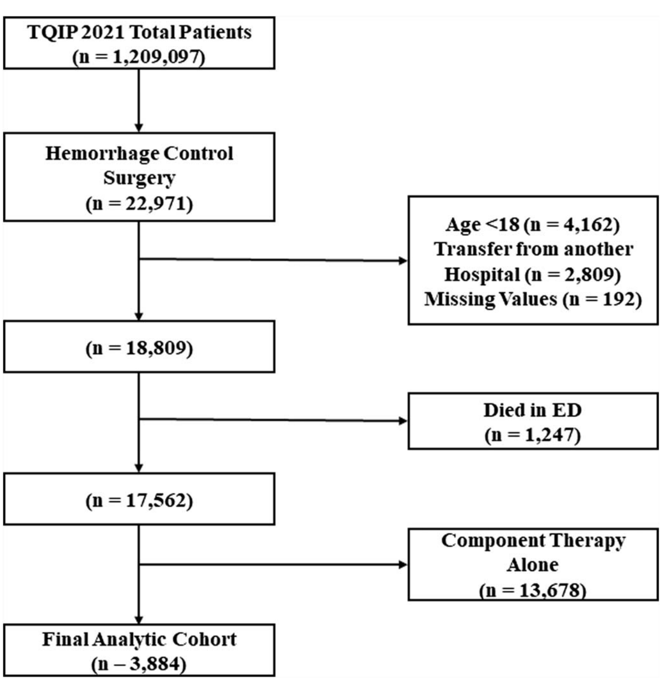

Figure 1. Flow diagram of patient's selection to reach our analytic sample.

DISCUSSION

In our analysis of the TQIP 2021 database in patients who received hemorrhage control surgery, we found that early resuscitation that was primarily centered on WB had a significant impact on mortality rate with improved survival in patients with lower ratios of pRBC to WB. Patients with higher pRBC/WB ratios had significantly higher adjusted hazard ratio of mortality at 24 hours.

Recently, several analyses have examined the effect of WB on morbidity and mortality in trauma resuscitation.[14–16] Using similar TQIP databases, Hanna et al.[14] and Torres et al.[15] found that WB decreased mortality in trauma patients presenting with hemorrhagic shock and who received MTP (4+ units of pRBC within 1 hour of arrival or >10 units of pRBC transfused at 24 hours of ED arrival). However, prior to 2020, WB administration was not precisely defined in TQIP and researchers relied on ICD10 coding to identify patients who received WB. This inherently prevented researchers from accurately calculating the volume of WB transfusion, and as a consequence, limited our ability to identify a relationship between pRBC/WB ratio and outcomes. Nonetheless, compared with CT alone, adding WB to the resuscitation protocols was associated with a statistically significant decrease in 24-hour mortality, in-hospital mortality, and major complications. In addition, Torres et al. (2023) demonstrated survival benefits of WB extending up to 30 days post-resuscitation.[15]

Previous studies that evaluated effectiveness of WB resuscitation lacked a direct comparison between WB alone and CT alone. This is understandable as WB supply has been, and still is limited.[8,17] As a result, most pre-hospital protocols and trauma centers, with some rare exceptions, have often limited the number of WB units transfused and often continued with CT afterwards. This was especially true in patients who required massive transfusion protocol (MTP). For example, at our academic Level I trauma center, we did not reach a reliable, adequate, and consistent supply of WB for several months after the initiation of our WB resuscitation protocol. Therefore, the currently available studies have only evaluated the additive effect of WB to CT. Naturally, the next question to be explored is whether the observed beneficial effect of WB is diluted when a large volume CT ensued. In the current analysis, we found that the risk of mortality at 24 hours in bleeding trauma patients who underwent hemorrhage control surgery decreased significantly with pRBC/WB ratio of 3:1 or less. It is also important to note that all transfusion ratio groups in our study patients received a balanced blood product resuscitation in addition to WB with a ratio of pRBC/FFP being on average 1:1. Although, platelet transfusion was variable among the groups, it appeared to actually increase with higher pRBC/WB transfusion, while survival diminished. The

TABLE 1. Characteristics of Patients Who Received WB Alone or With pRBC at Different Ratios

	Total	WB Only	1:1	2:1	3:1	4:1	5:1+	*p*
n	3,884	1,037 (26.7%)	469 (12.1%)	698 (18%)	436 (11.2%)	308 (7.9%)	936 (24.1%)	
Age, mean	39 ± 16	40 ± 16	40 ± 16	39 ± 16	40 ± 16	37 ± 15	39 ± 16	0.28
Male gender	3,208 (82.6%)	844 (81.4%)	379 (80.8%)	568 (81.4%)	359 (82.3%)	262 (85.1%)	796 (85%)	0.15
Race, Black	1,416 (36.5%)	341 (32.9%)	178 (38%)	256 (36.8%)	143 (32.8%)	121 (39.3%)	377 (40.3%)	0.008
SBP, mean	100 ± 37	110 ± 32	101 ± 35	102 ± 34	97 ± 37	92 ± 40	93 ± 43	0.0001
Lowest SBP	78 ± 40	89 ± 28	79 ± 29	79 ± 28	76 ± 27	71 ± 33	68 ± 34	0.0001
Heart rate	103 ± 36	101 ± 29	105 ± 34	107 ± 32	106 ± 36	103 ± 42	102 ± 44	0.01
SI > 1	1,549 (43.5%)	314 (31.5%)	197 (44.7%)	304 (46.1%)	196 (49%)	140 (51.9%)	398 (50.2%)	0.0001
BMI, mean	28.5 ± 12.1	28.8 ± 18	28.9 ± 9.8	28.3 ± 9.7	28.6 ± 6.6	28.9 ± 12.7	28 ± 6.4	0.87
GCS, median	14 (5–15)	15 (13–15)	14 (6–15)	14 (7–15)	14 (5–15)	14 (3–15)	12 (3–15)	0.0001
GCS < 8	1,137 (30%)	181 (17.7%)	126 (28.1%)	187 (27.4%)	132 (31.3%)	107 (36.2%)	404 (44.2%)	0.0001
WB units	2 (1–3)	2 (1–2)	4 (2–5)	2 (2–4)	2 (1–3)	2 (1–2)	2 (1–2)	0.0001
PRBC units	5 (2–11)	NA	1 (1–3)	3 (2–5)	4 (2–7)	6 (3–7)	13 (8–22)	0.0001
FFP units	2 (0–7)	0	1 (0–3)	2 (1–5)	3 (1–6)	5 (2–8)	12 (6–20)	0.0001
Platelet units	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–2)	0.0001
pRBC/FFP	1:1 (1:1–1:2)	NA	1:1 (1:1–1:1)	1:1 (1:1–1:1)	1:1 (1:1–2:1)	1:1 (1:1–1:2)	1:1 (1:1–1:2)	0.0001
pRBC/PLT	7:1 (5:1–11:1)	NA	2:1 (1:1–3:1)	5:1 (3:1–7:1)	5:1 (4:1–9:1)	6:1 (4:1–8:1)	8:1 (6:1–12:1)	0.0001
WB + PRBC, units	5 (3–11)	2 (1–2)	5 (3–7)	5 (4–9)	6 (3–10)	8 (4–9)	15 (10–24)	0.0001
Penetrating	2,026 (52.2%)	589 (56.8%)	255 (54.4%)	341 (48.9%)	200 (45.9%)	164 (53.3%)	477 (51%)	0.001
Hemorrhagic Injury								
Liver	1,104 (28.4%)	218 (21%)	130 (27.7%)	172 (24.6%)	116 (26.6%)	89 (28.9%)	379 (40.5%)	0.0001
Spleen	868 (22.4%)	172 (16.6%)	112 (23.9%)	148 (21.2%)	90 (20.6%)	78 (25.3%)	268 (28.6%)	0.0001
Pelvis	924 (23.8%)	189 (18.2%)	113 (24.1%)	172 (24.6%)	106 (24.3%)	81 (26.3%)	263 (28.1%)	0.0001
Renal	522 (13.4%)	105 (10.1%)	59 (12.6%)	93 (13.3%)	65 (14.9%)	42 (13.6%)	158 (16.9%)	0.001
Cardiac	238 (6.1%)	34 (3.3%)	29 (6.2%)	40 (5.7%)	24 (5.5%)	31 (10.1%)	80 (8.6%)	0.0001
Vascular	1,615 (41.6%)	336 (32.4%)	186 (39.7%)	280 (40.1%)	174 (39.9%)	135 (43.8%)	504 (53.8%)	0.0001
Hemothorax	444 (11.4%)	68 (6.6%)	61 (13%)	65 (9.3%)	48 (11%)	52 (16.9%)	150 (16%)	0.0001
Total injuries	1 (1–2)	1 (0–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	2 (1–3)	0.0001
ISS, median	25 (16–34)	17 (10–26)	25 (16–34)	22 (14–34)	22 (16–35)	26 (17–38)	29 (21–41	0.0001
ISS > 25	1, 953 (50.3%)	331 (31.9%)	243 (51.8%)	343 (49.1%)	213 (48.9%)	185 (60.1%)	638 (68.2%)	0.0001
NISS, median	38 (26–54)	29 (17–43)	38 (27–50)	36 (24–50)	41 (27–57)	41 (27–57)	48 (34–59)	0.0001
Hemorrhage control surgery								0.0001
Laparotomy	2,299 (59.2%)	549 (52.9%)	293 (62.5%)	396 (56.7%)	265 (60.8%)	170 (55.2%)	626 (66.9%)	
Thoracotomy	491 (12.6%)	65 (6.3%)	60 (12.8%)	80 (11.5%)	58 (13.3%)	60 (19.5%)	168 (18%)	
Sternotomy	64 (1.6%)	11 (1.1%)	8 (1.7%)	10 (1.4%)	6 (1.4%)	9 (2.9%)	20 (2.1%)	
Pelvic packing	39 (1%)	4 (0.4%)	3 (0.6%)	8 (1.2%)	6 (1.4%)	9 (2.9%)	20 (2.1%0	
Extremity	515 (13.3%)	213 (20.5%)	59 (12.6%)	96 (13.7%)	55 (12.6%)	37 (12%)	55 (5.9%)	
Other	476 (12.3%)	195 (18.8%)	46 (9.8%)	108 (15.5%)	46 (10.6%)	27 (8.85)	54 (5.8%)	
Time to hemorrhage control, min	53 (31–106)	65 (35–150)	53 (30–104)	58 (33–128)	58 (33–106)	53 (30–98)	41 (27–72)	0.0001

Data are presented as counts and percentages, median with IQR, or means with standard deviation.
GCS, Glasgow Coma Scale; ISS, Injury Severity Score; NISS, New Injury Severity Score; SBP, systolic blood pressure; SI, shock index.

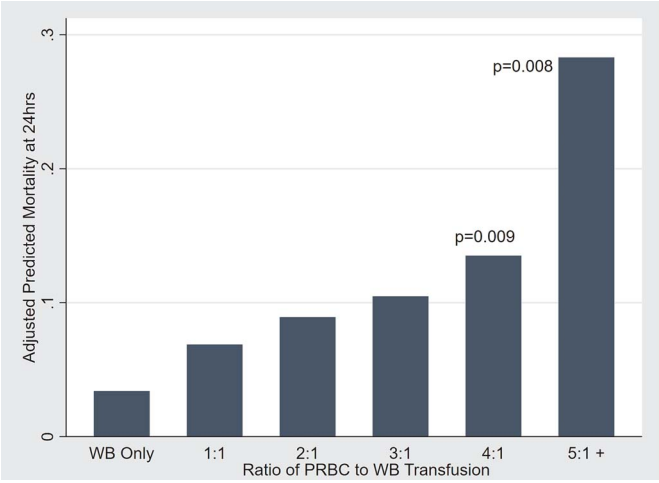

Figure 2. Adjusted mortality rates among different transfusion ratio groups. *p* Values indicate direct comparison to WB only group.

difference in platelet units transfused could be explained by the "catching-up" approach with large volume transfusions. Yet, the survival benefits of platelet transfusion seem to be more apparent when resuscitation relied primarily on WB, which inherently guarantees platelets transfusion. This further supports that beneficial effect of WB-centered resuscitation on mortality.

When examining prior analyses of WB resuscitation in trauma, we found that many did not remain below the desired ratio of pRBC to WB that we identified in this study. In the study by Yazer et al.,[19] patients received up to two units of WB (average, 1.74 units per patient) in the intervention arm. However, these patients also received on average greater than 10 units of pRBC, which far exceeds our established cutoff of a 3:1 ratio.[19] This may explain the lack of mortality benefit seen in their study. A similar result was reported by Hazelton et al.,[21] where a majority of patients in the WB group received only 1 unit of WB but received a median of 4 units of PRBC at 24 hours Again, this ratio is above the cutoff ratio that we observed to provide a WB benefit, which may explain the lack of benefit in mortality found in the study.[21] Despite this, we ought to be cautious when comparing our analyses to the prior studies. Prior studies utilized 24-hour data on blood products administration where the current analysis was limited to blood products given in the first 4 hours, due to available data in TQIP. We are not able to assess whether these ratios changed when blood product resuscitation continued beyond the initial 4 hours. Therefore, future examinations should seek to further examine the effect of WB dilution on hemorrhagic resuscitation beyond 4 hours. Gallaher et al.[12] compared component therapy resuscitation to that with added WB transfusion, but in terms of component-equivalent units. They showed that WB transfusion resulted in more balanced resuscitation and was feasible and safe, even in large volume. Even though this supports being more liberal in WB transfusions, it equates the value of WB and CT, as it evaluates WB as a sum of its parts. Others have demonstrated a better hemostatic profile of WB compared with balanced component therapy.[11] Based on our results and previous work, we think that *maintaining* a balanced ratio of pRBC and WB throughout trauma resuscitation (at or below 3:1 ratio) may have a survival benefit and should be further validated.

In observing that many of the prior examinations of WB do not reach the 3:1 ratio established by the current analysis, we must consider both the supply element and the clinical setting limitations in the delivery of lower pRBC to WB ratios. Whole blood requires increased resources for preservation and maintenance of the blood product compared with pRBC. Donors of WB must meet stringent requirements and the WB must be processed within 8 hours of donation.[8] Therefore, due to the increased resource allocation necessary, many centers limit their use of WB per patient.[17] This limited supply and rationing of WB may precipitate inequities in benefits provided by WB use and should be further examined in future works. Moreover, in the case of high-volume transfusions it may be practically difficult to maintain our cutoff ratio. This may be especially true in cases of ultra-massive transfusions, when patients receive greater or equal to 20 units of pRBC in 24 hours.[22,23] This could be due to limited supply or complete consumption of WB resources resulting in continued resuscitation with products only and subsequently a higher ratio. Interestingly, the limited supply does not seem to correlate with higher costs for WB transfusion in the prehospital

TABLE 2. Differences in Outcomes Among the Different Ratio Groups

Outcomes	All n = 3,884	WB n = 1,037	1:1 n = 469	2:1 n = 698	3:1 n = 436	4:1 n = 308	5:1+ n = 936	*p*
Death 24 h	635 (16.4%)	54 (5.2%)	51 (10.9%)	82 (11.8%)	65 (14.9%)	64 (20.9%)	319 (34.1%)	0.0001
In-hospital mortality	955 (24.6%)	94 (9.1%)	77 (16.4%)	145 (20.8%)	102 (23.5%)	80 (26.1%)	457 (48.8%)	0.0001
Hospital LOS, median	11 (4–22)	9 (5–18)	13 (6–24)	11 (6–23)	12 (5–23)	11 (4–26)	9 (2–24)	0.0001
ARDS	72 (2.2%)	8 (0.8%)	10 (2.4%)	12 (1.9%)	8 (2.1%)	11 (4.5%)	23 (3.7%)	0.001
AKI	205 (6.3%)	15 (1.5%)	17 (4.1%)	41 (6.7%)	14 (3.8%)	21 (8.6%)	97 (15.7%)	0.0001
Severe sepsis	87 (2.7%)	8 (0.8%)	11 (2.6%)	20 (3.3%)	7 (1.9%)	10 (4.1%)	31 (5%)	0.0001
DVT	185 (5.7%)	23 (2.6%)	27 (6.5%)	35 (5.7%)	22 (5.9%)	17 (7%)	61 (9.9%)	0.0001
Unplanned ICU admission	192 (5.9%)	43 (4.4%)	30 (7.2%)	32 (5.2%)	21 (5.7%)	19 (7.8%)	47 (7.6%)	0.06
Unplanned intubation	143 (4.4%)	28 (2.9%)	19 (4.6%)	27 (4.4%)	18 (4.9%)	15 (6.2%)	36 (5.8%)	0.06
Pneumonia	114 (3.5%)	13 (1.3%)	13 (3.1%)	18 (2.9%)	20 (5.4%)	19 (7.8%)	31 (5%)	0.0001
Decubitus ulcer	107 (3.3%)	14 (1.4%)	10 (2.4%)	26 (4.2%)	11 (3%)	16 (6.6%)	30 (4.9%)	0.0001
Unplanned return to operating room	393 (10.1%)	64 (6.2%)	43 (9.2%)	61 (8.7%)	50 (11.5%)	42 (13.6%)	133 (13.2%)	0.0001

Data are presented as counts and percentages, unless otherwise specified.
LOS, length of stay; ARDS, acute respiratory distress syndrome, AKI, acute kidney injury, DVT, deep venous thrombosis; ICU, intensive care unit.

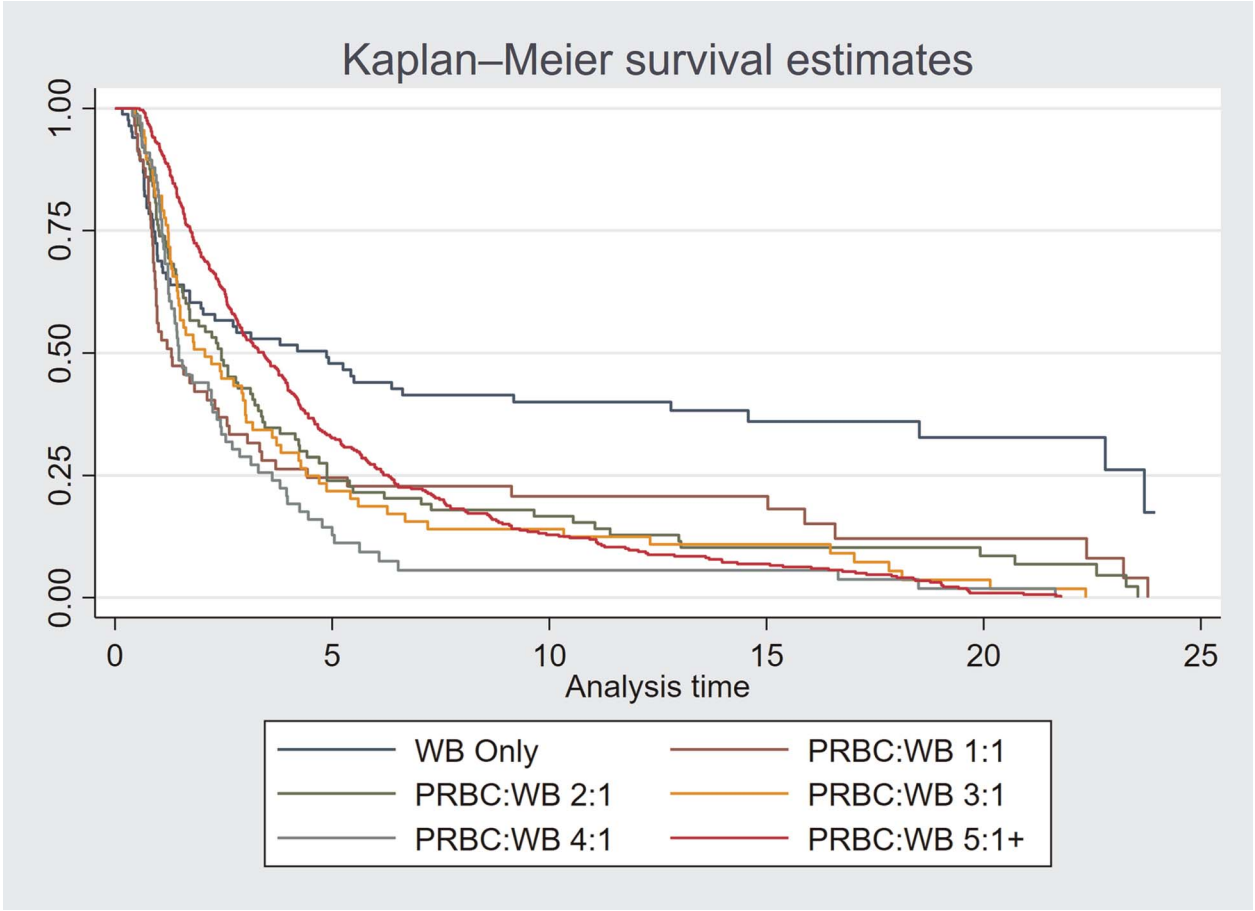

Figure 3. Kaplan-Meier survival curves for different transfusion ratio groups.

settings.[24] Ultimately, local resources, policies and practices impact choices of transfusion protocols. Nonetheless, our findings, along with the complex nature of the supply process of WB, may lead to preferentially delegating WB to patients that could receive the most benefit.

Our Cox regression analysis indicated a higher HR of mortality in the 3:1 ratio group, which seems to be incongruent with our multiple logistic regression results (Table 3). We think this difference is due to the consideration of time-to-death in the Cox regression and that the true optimal cutoff is likely just below 3:1 ratio. However, our preference is to remain conservative in our interpretation of these results. Therefore, we identified 3:1 as an optimal transfusion ratio.

We observed a significantly higher rates of complications in patients who received higher transfusion ratios early in their resuscitation. However, these findings should be considered exploratory as we did not perform adjusted analysis on secondary outcomes. It is important that these associations be further examined to evaluate the true impact of resuscitation on complications. For instance, we observed a higher rate of unplanned return to the operating room in higher ratio groups. While this could reflect the higher injury severity in these groups, we may consider the role of coagulopathy secondary to the resuscitation practices that do not incorporate adequate WB transfusion, which may result in a delay in achieving hemorrhage control.

The major limitation of our examination is the utilization of a large multicenter dataset. In using the TQIP database, there is a lack of standardization of data submission between participating centers, which could produce information bias. Further, data on blood products was only available for the first 4 hours of the encounters. This limits our findings to encompass only blood product utilization in the acute period of resuscitation. Therefore, we are unable to assess how the ratios changed beyond the 4-hour

TABLE 3. Results of Adjusted Regression Analysis and Cox Regression Analysis Depicting ORs and HRs of 24-h Mortality, Respectively, Among Different Ratio Groups Compared With Whole Blood Only Group

Group	OR	95% CI	HR	95% CI
WB only	Reference		Reference	
1:1	0.74	0.28–1.95	1.65	0.64–4.27
2:1	1.61	0.70–3.74	1.27	0.58–2.79
3:1	1.37	0.56–3.37	2.83	1.18–6.77
4:1	2.85	1.19–6.81	3.67	1.57–8.57
5:1 +	2.89	1.29–6.49	1.97	0.91–4.23

Both analyses were adjusted for patients' age, sex, injury severity, penetrating injury, depressed mental status, shock index on presentation, total number of units transfused, type of hemorrhage control surgery, and time to hemorrhage control surgery.

time point and how that impacted survival. For example, a computed ratio in the first 4 hours could later become either higher, due to limiting WB transfusion or consumption of WB products, or lower, if "catching-up" with WB occurred after 4 hours. In addition, we are not able to assess the dynamic change in transfusion administration and ratios, even within the first 4 hours. Despite that, there is an advantage by using 2021 TQIP database as it provided volume of transfusions in mL allowing us to carefully examine the different ratios in early resuscitation. We are unable to control all possible confounders due to the lack of control over data collection. However, we attempted to control for statistically and clinically relevant factors, including total volume of resuscitation, time to hemorrhage control surgery, and hemodynamic status at time of presentation. The goodness-of-fit test shows a fit model, although we believe that more granular data should allow for a better identification of the true effect of pRBC/WB ratio on outcomes. Despite our careful adjustments to have clinically comparable groups, there might still be unmeasured characteristics that make our groups different, and therefore directly impact our results. This is more probable in the extremes of the groups (WB only and 5:1 ratio groups). To control for this, we repeated the multivariable regression analysis changing the reference value of the ratio groups (Supplemental Material, http://links.lww.com/TA/D438). Compared with 1:1 ratio group, higher ratio groups continued to have a higher OR of mortality. Nonetheless, future prospective validation of these results would ensure adequate control for clinical variables to minimize variability among groups and better identify the true estimates of mortality. Trauma Quality Improvement Program does not provide physiologic data beyond admission data. Therefore, we are not able to assess differences in endpoints of resuscitation. Similarly, we cannot assess when hemorrhage control was achieved, only when hemorrhage control surgery began. Intra-operative death was not reported either. These factors are vital when assessing mortality following hemorrhage control. Further, our population was limited to patients receiving hemorrhage control surgery. This limits our generalizability since most resuscitation protocols initiate blood product transfusion when a hemorrhagic injury is suspected, but not necessarily proven. Patients might receive early WB transfusion for hypotension but not require further transfusion if the cause of hypotension is determined to be non-hemorrhagic. By narrowing our cohort to patients who only underwent hemorrhage control surgery, we attempted to minimize the survival bias of including patients who only received WB but did not end up with a life-threatening hemorrhage. Finally, we converted mL to units based upon the commonly applied blood bank and transfusion standards for different blood products.[20] Variations in blood product preparations might result in a different categorization of units transfused or the calculated ratios. However, we believe this to be of a minimal effect. Nonetheless, our finding of an optimal ratio may need to be extrapolated to meet center specific volume standards for blood products.

CONCLUSION

Using the TQIP 2021 database, we concluded that lower ratios of pRBC to WB resuscitation given in the first 4 hours were associated with improved survival at 24 hours. We identified an optimal ratio of 3:1 or less as a potential target in ongoing trauma resuscitations. We acknowledge that major variations in supply and demand exist among different trauma systems; however, we recommend providers be cognizant of this relationship and maintain a balanced WB resuscitation to prevent dilution of its effect in massive transfusion scenarios. Future studies should examine WB ratios prospectively in order to ensure clinical comparability among groups to determine causality while factoring in the limited supply of WB.

AUTHORSHIP

G.J.F. participated in the study design, data analysis and interpretation, article preparation, critical revisions. A.C.T., M.L.P., B.E., S.N.L., A.M.H. participated in the article preparation, critical revisions. T.K. participated in the study conception and design, data analysis and interpretation, article preparation, critical revisions.

DISCLOSURE

None of the authors have any conflict of interest to report. All JTACS Disclosure forms have been supplied and are provided as supplemental digital content (http://links.lww.com/TA/D439).
Conflict of interest statements for all the authors.

REFERENCES

1. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2017;82(3):605–617.
2. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1: 1: 1 vs a 1: 1: 2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471–482.
3. Holcomb JB, Del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg*. 2013;148(2):127–136.
4. Hynes AM, Geng Z, Schmulevich D, Fox EE, Meador CL, Scantling DR, et al. Staying on target: maintaining a balanced resuscitation during damage-control resuscitation improves survival. *J Trauma Acute Care Surg*. 2021;91(5):841–848.
5. Davenport RA, Brohi K. Cause of trauma-induced coagulopathy. *Current Opinion in Anesthesiology*. 2016;29(2):212–219.
6. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17:R76.
7. MacKay EJ, Stubna MD, Holena DN, Reilly PM, Seamon MJ, Smith BP, et al. Abnormal calcium levels during trauma resuscitation are associated with increased mortality, increased blood product use, and greater hospital resource consumption: a pilot investigation. *Anesth Analg*. 2017;125(3):895–901.
8. Godbey EA. Whole blood transfusion: past, present, and future. *Clin Lab Med*. 2021;41(4):659–667.
9. Yazer MH, Cap AP, Spinella PC. Raising the standards on whole blood. *J Trauma Acute Care Surg*. 2018;84(6S):S14–S17.
10. Hall S, Murphy M. *Limitations of component therapy for massive haemorrhage: is whole blood the whole solution?* Wiley Online Library; 2015:511–514.
11. Kornblith LZ, Howard BM, Cheung CK, Dayter Y, Pandey S, Busch MP, et al. The whole is greater than the sum of its parts: hemostatic profiles of whole blood variants. *J Trauma Acute Care Surg*. 2014;77(6):818–827.
12. Gallaher JR, Dixon A, Cockcroft A, Grey M, Dewey E, Goodman A, et al. Large volume transfusion with whole blood is safe compared with component therapy. *J Trauma Acute Care Surg*. 2020;89(1):238–245.
13. Williams J, Merutka N, Meyer D, Bai Y, Prater S, Cabrera R, et al. Safety profile and impact of low-titer group O whole blood for emergency use in trauma. *J Trauma Acute Care Surg*. 2020;88(1):87–93.
14. Hanna K, Bible L, Chehab M, Asmar S, Douglas M, Ditillo M, et al. Nationwide analysis of whole blood hemostatic resuscitation in civilian trauma. *J Trauma Acute Care Surg*. 2020;89(2):329–335.
15. Torres CM, Kent A, Scantling D, Joseph B, Haut ER, Sakran JV. Association of whole blood with survival among patients presenting with severe

hemorrhage in US and Canadian adult civilian trauma centers. *JAMA Surg*. 2023;158:532.
16. Hazelton JP, Ssentongo AE, Oh JS, Ssentongo P, Seamon MJ, Byrne JP, et al. Use of cold-stored whole blood is associated with improved mortality in hemostatic resuscitation of major bleeding: a multicenter study. *Ann Surg*. 2022;276(4):579–588.
17. Yazer MH, Spinella PC. An international survey on the use of low titer group O whole blood for the resuscitation of civilian trauma patients in 2020. *Transfusion*. 2020;60:S176–S179.
18. Ruby KN, Dzik WH, Collins JJ, Eliason K, Makar RS. Emergency transfusion with whole blood versus packed red blood cells: a study of 1400 patients. *Transfusion*. 2023;63:745–754.
19. Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. *J Trauma Acute Care Surg*. 2016;81(1):21–26.
20. Strauss DM. Component Preparation and Manufacturing. In: Shaz BH, Morayma RG, Hillyer CD, eds. *Transfusion medicine and hemostasis: clinical and laboratory aspects*. 3rd ed. Cambridge, MA, USA: Elsevier Inc.; 2019:53–58.
21. Hazelton JP, Cannon JW, Zatorski C, Roman JS, Moore SA, Young AJ, et al. Cold-stored whole blood: a better method of trauma resuscitation? *J Trauma Acute Care Surg*. 2019;87(5):1035–1041.
22. Velmahos GC, Chan L, Chan M, Tatevossian R, Cornwell EE 3rd, Asensio JA, et al. Is there a limit to massive blood transfusion after severe trauma? *Arch Surg*. 1998;133(9):947–952.
23. Quintana MT, Zebley JA, Vincent A, Chang P, Estroff J, Sarani B, et al. Cresting mortality: defining a plateau in ongoing massive transfusion. *J Trauma Acute Care Surg*. 2022;93(1):43–51.
24. Ciaraglia A, Myers JC, Braverman M, Barry J, Eastridge B, Stewart R, et al. Transfusion-related cost comparison of trauma patients receiving whole blood versus component therapy. *J Trauma Acute Care Surg*. 2023;95(1):62–68.