

Preferential whole blood transfusion during the early resuscitation period is associated with decreased mortality and transfusion requirements in traumatically injured patients

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ABSTRACT

Introduction Whole blood (WB) transfusion represents a promising resuscitation strategy for trauma patients. However, a paucity of data surrounding the optimal incorporation of WB into resuscitation strategies persists. We hypothesized that traumatically injured patients who received a greater proportion of WB compared with blood product components during their resuscitative efforts would have improved early mortality outcomes and decreased transfusion requirements compared with those who received a greater proportion of blood product components.

Methods Retrospective review from our Level 1 trauma center of trauma patients during their initial resuscitation (2019–2022) was performed. WB to packed red blood cell ratios (WB:RBC) were assigned to patients based on their respective blood product resuscitation at 1, 2, 3, and 24 hours from presentation. Multivariable regression models were constructed to assess the relationship of WB:RBC to 4 and 24-hour mortality, and 24-hour transfusion requirements.

Results 390 patients were evaluated (79% male, median age of 33 years old, 48% penetrating injury rate, and a median Injury Severity Score of 27). Overall mortality at 4 hours was 9%, while 24-hour mortality was 12%. A significantly decreased 4-hour mortality was demonstrated in patients who displayed a WB:RBC \geq 1 at 1 hour (5.9% vs. 12.3%; OR 0.17, $p=0.015$), 2 hours (5.5% vs. 13%; OR 0.16, $p=0.019$), and 3 hours (5.5% vs. 13%, OR 0.18, $p<0.01$), while a decreased 24-hour mortality was displayed in those with a WB:RBC \geq 1 at 24 hours (7.9% vs. 14.6%, OR 0.21, $p=0.01$). Overall 24-hour transfusion requirements were significantly decreased within the WB:RBC \geq 1 cohort (12.1 units vs. 24.4 units, $p<0.01$).

Conclusion Preferential WB transfusion compared with a balanced transfusion strategy during the early resuscitative period was associated with a lower 4 and 24-hour mortality, as well as decreased 24-hour transfusion requirements, in trauma patients. Future prospective studies are warranted to determine the optimal use of WB in trauma.

Level of evidence Level III/therapeutic

BACKGROUND

Acute resuscitation for hemorrhagic shock remains a highly evolving field and active focus for both

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incorporation of whole blood into massive transfusion protocols has demonstrated improved mortality in military and civilian data.

WHAT THIS STUDY ADDS

⇒ Transfusing whole blood at a ratio greater than blood components during resuscitative efforts in traumatically injured patients may reduce mortality and transfusion requirements.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings are the first to assess how whole blood is transfused compared with blood component transfusions and offer a novel approach for future studies that should be explored prospectively to optimize our transfusion strategies.

military and civilian trauma research. Military data from recent conflicts initially described the concept of damage control resuscitation (DCR).^{1 2} DCR, which aims to minimize crystalloid use, target a hypotensive resuscitation, and use a balanced blood product resuscitation strategy, has become the standard approach in combat settings as the ideal strategy to help augment damage control surgery.^{1 3} These concepts have subsequently been adapted into civilian practice after a multitude of prospective studies demonstrating numerous benefits associated with various DCR principles.^{4 5}

As the military conflicts within the Middle East progressed, whole blood (WB) transfusion strategies became common practice for combat casualties due to the inherent logistical difficulties associated with blood component storage in the deployed environment.^{6–10} Analogous to the civilian adoption of DCR, WB transfusions have become increasingly used within the civilian sector.^{11 12} To date, civilian data assessing the use of WB remain largely limited to a handful of observational studies. These studies, however, have demonstrated varying degrees of survival benefit in traumatically injured patients when WB was incorporated into massive transfusion protocols (MTP).^{13–15}

Although the recent civilian studies assessing WB have been promising, these studies were designed

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To cite: Lammers D, Hu P, Rokayak O, et al. *Trauma Surg Acute Care Open* 2024;**9**:e001358.

to only assess the impact of incorporating WB into MTP. This dichotomous categorization of WB use results in an inability to assess the relationship of how WB was used compared with the other respective transfused blood components. It remains biologically plausible that the impact of WB during massive transfusion varies per patient depending on injury patterns, and degree of shock or coagulopathy present, as well as their resuscitation requirements. In our current study, we sought to assess the relationship between WB transfusions and a balanced blood component resuscitation strategy for patients receiving both WB and blood components during their early resuscitative efforts. We hypothesized that trauma patients at risk for hemorrhagic shock who received a higher ratio of WB compared with their respective balanced transfusion requirements during the initial resuscitation period would have improved early mortality outcomes and lower transfusion needs compared with those who received a greater ratio of blood component therapy.

METHODS

A retrospective review of the internal trauma registry at a single American College of Surgeons-verified Level 1 trauma center between 2019 and 2022 was performed for all non-transfer trauma patients who arrived with pulses and did not receive a resuscitative thoracotomy. The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

To identify patients at risk for death secondary to hemorrhagic shock and mitigate risks of including those who experienced death secondary to other potential early causes of mortality within trauma patients, those who were severely injured, met the blood transfusion critical administration threshold (CAT) within the first hour of arrival, and did not have a severe traumatic brain injury (TBI) were assessed for this analysis. Severe injury was defined as an Injury Severity Score (ISS) greater than 15, CAT was defined as receiving three or more units of red blood cell (RBC) containing blood products (packed RBC (pRBC) or WB), and severe TBI was defined as a head Abbreviated Injury Score (AIS1) greater than 3.^{16,17} Pediatric patients, defined within our analysis as patients less than 18 years of age, were excluded from this analysis. Encompassed within the database are demographic data such as age, sex, mechanism of injury, and trauma-related outcome data such as ISS, AIS, mortality, and transfusion requirements, as well as physiologic data to include basic laboratory values and vital signs. Each unique patient identification number was evaluated to assure no redundancies were present within the data set.

The volume of transfused blood products, to include units of pRBC, fresh frozen plasma (FFP), platelets (PLT), and WB, was evaluated for all patients found to meet the inclusion criteria. Institutional guidelines at our trauma center recommend the use of WB or balanced transfusions (ie, equal portions of pRBC, FFP, and PLT) when blood components are used for trauma resuscitation. With regard to WB, low-titer cold-stored type O WB represents our institutional transfusion practice during the initial resuscitation when WB is used. Similarly, uncrossed universal blood components are used initially when components are transfused. A crossmatch is performed during the first set of arrival trauma labs and attempts are made to transition to type-specific products once these data are available. During the time of this study, the decision to transfuse WB or blood component therapy was guided by the bedside clinician.

To compare the relationship of WB with a balanced transfusion, a ratio of the units of WB to pRBC (WB:RBC) that were

transfused was created for each patient. pRBC was used as a surrogate for a balanced transfusion after assuring balanced transfusions were clinically performed in accordance with our guidelines. Ratios for the total patient population were assessed at 1, 2, 3, and 24 hours from arrival to the trauma bay. Patients were stratified into two groups at each respective time period: those with a high WB:RBC ratio (ie, WB:RBC \geq 1) and those with a low ratio (WB:RBC $<$ 1). Primary outcomes of interest included 4 and 24-hour mortality, with secondary outcomes assessing volume of transfused blood products at each time point assessed (figure 1).

Descriptive statistical analysis was performed for all patients included within the investigation and presented as frequencies, means, or medians, as appropriate. Univariate analysis was performed between the high WB:RBC cohort and the low WB:RBC cohort. Categorical and continuous variables were compared via χ^2 analysis and Student's t-test or Mann-Whitney U test, respectively. Multivariable logistic regression taking into account factors that were different between baseline groups was then used to identify variables independently associated with mortality outcomes via adjusted ORs. Secondary outcomes assessed transfusion requirements. P values of less than or equal to 0.05 were considered statistically significant for all tests performed. All statistical analyses were performed using IBM SPSS V.28 (Armonk, NY).

RESULTS

A total of 390 patients were evaluated based on our inclusion criteria. The study population was largely male (79%), with a median age of 33, and sustained a penetrating injury as the primary mechanism of injury 48% of the time. All patients evaluated were brought to the trauma bay directly from the scene of injury. On arrival the median heart rate was 118 beats per minute, median blood pressure was 96 mm Hg, and the median Glasgow Coma Scale (GCS) score was 14. Within the first 24 hours, two-thirds of the patients received at least one unit of WB. The overall median ISS was 27 and the overall mortality at 4 and 24 hours was 9% and 12%, respectively. The overall demographics can be seen in table 1.

To use pRBC as a surrogate for balanced transfusions, overall blood product transfusions were assessed at all time points within the study. Based on mean and median blood products transfused, a balanced strategy was by and large present within the study population, indicating that transfusion practices were in accordance with our institutional guidelines. Overall transfused blood products, including WB, are demonstrated in table 2. A WB:RBC \geq 1 was present in roughly half of the patient population at 1, 2, and 3 hours from arrival, with 39% of patients displaying a WB:RBC \geq 1 at 24 hours (table 1).

At each of the various time points assessed, patients within the high WB:RBC ratio cohort demonstrated baseline differences in presentation demographics and physiology when compared with those within the low ratio cohort (table 3). At 1 hour from arrival, patients within the high ratio cohort were more likely to be tachycardic and have sustained a penetrating mechanism of injury. Patients within the high ratio cohort were once again more likely to be tachycardic on arrival when assessed at 2 hours; however, there were no statistically significant differences between the cohorts when assessed at 3 or 24 hours from arrival.

On univariate analysis, the high ratio cohort displayed lower 4 and 24-hour mortality when compared with the low ratio cohort (table 3). Four-hour mortality was statistically lower for those patients within high ratio cohort at 1 hour (5.9%

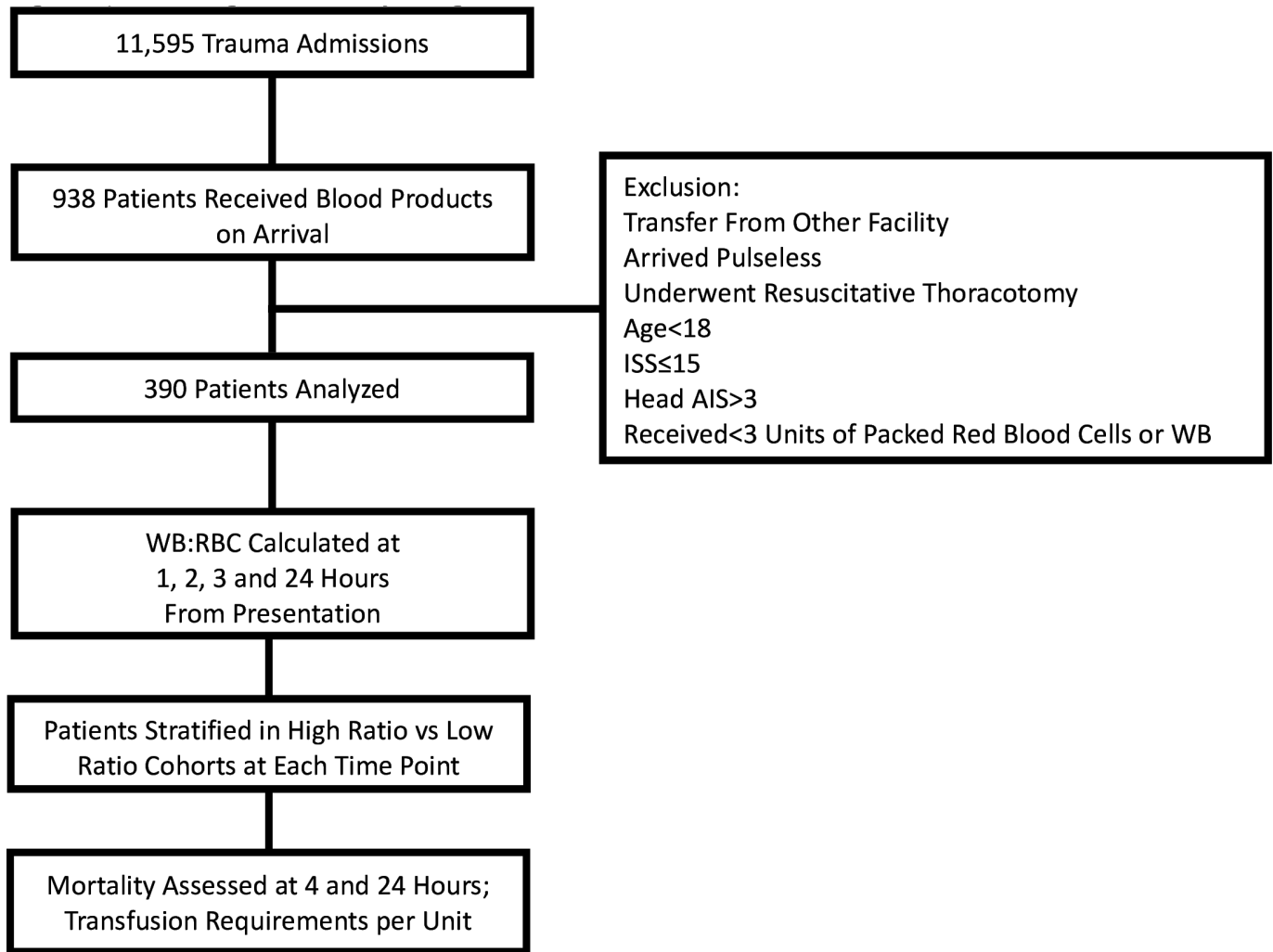


Figure 1 Flow diagram of study design. AIS, Abbreviated Injury Score; ISS, Injury Severity Score; WB:RBC, whole blood to packed red blood cell ratio.

Table 1 Overall patient demographics

Variable	Total (n=390)
Age	33
Male, n (%)	308 (79)
Caucasian, n (%)	172 (44)
ISS	27
Penetrating, n (%)	186 (48)
HR on arrival	118
SBP on arrival	96 mm Hg
GCS on arrival	14
Received WB within first 24 h, n (%)	260 (66.67)
WB:RBC≥1, n (%)	
1 h	170 (44)
2 h	182 (47)
3 h	183 (47)
24 h	151 (39)
Mortality, n (%)	
4h	37 (9)
24 h	47 (12)

GCS, Glasgow Coma Scale; HR, heart rate; ISS, Injury Severity Score; SBP, systolic blood pressure; WB:RBC, whole blood to packed red blood cell ratio.

vs. 12.3%, $p=0.04$), 2 hours (5.5% vs. 13%, $p=0.02$) and 3 hours (5.5% vs. 13%, $p=0.01$) from arrival. Similarly, 24-hour mortality was significantly lower within patients in the high ratio cohort at 1 hour (8.2% vs. 15%, $p=0.04$), 2 hours (6.8% vs. 16.8%, $p<0.01$), 3 hours (6.8% vs. 16.9%, $p<0.01$), and 24 hours (7.9% vs. 14.6, $p=0.048$). This decreased mortality was further confirmed on multivariable analysis. After adjusting for mechanism of injury, heart rate on arrival, systolic blood pressure on arrival, GCS on arrival, and ISS, a WB:RBC≥1 was independently associated with improved 4-hour mortality when models were assessed for patient cohorts at 1 hour (OR 0.17, 95% CI 0.04 to 0.70; $p=0.02$), 2 hours (OR 0.19, 95% CI 0.05 to 0.76; $p=0.02$), and 3 hours (OR 0.18, 95% CI 0.05 to 0.75;

Table 2 Mean and median transfusion requirements

Time (h)	Mean				Median			
	RBC	FFP	PLT	WB	RBC	FFP	PLT	WB
1	3.66	3.39	0.26	2.32	2	2	0	1.5
2	5.25	4.87	0.47	3.06	3	3	0	2
3	6.02	5.59	0.63	3.22	3	3	0	2
24	7.78	7.41	1.21	3.26	5	4	1	2

FFP, fresh frozen plasma; PLT, platelets; RBC, red blood cells; WB, whole blood.

Table 3 Univariate analysis comparing study cohorts during the first 24 h

Variable	1 h			2 h			3 h			24 h		
	WB:RBC<1 (n=220)	WB:RBC≥1 (n=170)	P value	WB:RBC<1 (n=208)	WB:RBC≥1 (n=182)	P value	WB:RBC<1 (n=207)	WB:RBC≥1 (n=183)	P value	WB:RBC<1 (n=239)	WB:RBC≥1 (n=118)	P value
Age	39	37	0.325	39	37	0.170	39	37	0.209	39	36	0.073
Male, n (%)	170 (77.3)	138 (81.2)	0.382	165 (79.3)	143 (78.6)	0.901	168 (80.2)	142 (77.6)	0.536	190 (79.5)	118 (78.1)	0.799
Caucasian, n (%)	107 (48.6)	65 (38.2)	0.123	100 (48.1)	72 (39.6)	0.248	98 (47.3)	74 (40.4)	0.357	111 (46.4)	61 (40.4)	0.225
ISS	28.8	28.2	0.585	28.5	28.7	0.803	28.5	28.7	0.840	28.7	28.3	0.706
Penetrating, n (%)	91 (41.2)	95 (55.9)	0.006	92 (44.2)	94 (51.6)	0.156	93 (44.9)	93 (50.8)	0.265	108 (45.2)	78 (51.7)	0.252
HR on arrival	111	118	0.021	112	118	0.040	112	117	0.060	114	116	0.421
SBP on arrival	100	103	0.352	100	102	0.466	99.5	103	0.241	100	103	0.302
GCS on arrival	11	10.5	0.315	10.9	10.7	0.659	10.9	10.8	0.895	10.8	10.9	0.900
Mortality, n (%)												
4 h	27 (12.3)	10 (5.9)	0.037	27 (13)	10 (5.5)	0.015	27 (13)	10 (5.5)	0.014	-	-	-
24 h	33 (15)	14 (8.2)	0.043	35 (16.8)	12 (6.6)	0.003	35 (16.9)	12 (6.6)	0.002	35 (14.6)	12 (7.9)	0.048

GCS, Glasgow Coma Scale; HR, heart rate; ISS, Injury Severity Score; SBP, systolic blood pressure; WB:RBC, whole blood to packed red blood cell ratio.

p=0.02) from arrival. 24-hour mortality demonstrated similar findings for the high ratio cohort at 1 hour (OR 0.27, 95% CI 0.09 to 0.78; p=0.02), 2 hours (OR 0.15, 95% CI 0.04 to 0.53; p<0.01), 3 hours (OR 0.15, 95% CI 0.04 to 0.52; p<0.01), and 24 hours (OR 0.21, 95% CI 0.06 to 0.72; p=0.01) from presentation. Multivariable regression results can be viewed in [table 4](#).

In addition to mortality differences, transfusion requirements were assessed. On average, the high ratio cohort displayed increased amounts of WB transfused at the 1, 2, 3, and 24-hour time periods. Conversely, mean blood component requirements, to include pRBC, FFP, and PLT, were significantly lower at all time periods assessed within the high ratio cohort compared with the low ratio cohort. Importantly, the average combined total units of blood products and WB transfused at 1, 2, 3, and 24 hours were significantly less for patients within the WB:RBC≥1 group. These findings can be found in [table 5](#).

DISCUSSION

The incorporation of WB into civilian resuscitation practices for trauma patients in hemorrhagic shock represents an increasingly used strategy.^{11 12} While the current data in favor of incorporating WB into MTP are promising, optimal practices for incorporating WB into standard resuscitation strategies have yet to be elucidated. This study sought to further expand on the current body of literature surrounding WB's use in trauma by assessing how WB was used in patients who received it, as opposed to whether WB was used or not. By doing so, we demonstrated that preferentially transfusing WB at a higher or equal ratio to a balanced transfusion strategy was associated with improved 4 and 24-hour mortality for trauma patients in hemorrhagic shock, as well as significantly decreased transfusion requirements. To our knowledge, this is the first civilian study to assess how WB is used during the trauma resuscitation in efforts to optimize transfusion patterns. Moreover, this represents the first civilian analysis to evaluate the ratio of WB transfused compared with a balanced transfusion strategy.

Advancements in resuscitation and transfusion practices have helped to shape the current standards of care for trauma patients requiring blood products. Balanced blood component ratios have been regarded as the standard of care during DCR; although, incorporating WB into DCR represents a paradigm shift in current practice.¹⁸⁻²⁰ Balanced blood product transfusions seek to mimic WB by recapitulating its constituents; however, one unit of WB offers substantially higher concentrations of hematocrit, coagulation factors, fibrinogen, and PLT when compared with respective individual blood components.²¹

Similar to our current study, Gurney *et al* demonstrated an 88% reduction in 6-hour mortality for combat casualties who received at least one-third of their red cell containing transfusion via warm fresh whole blood (WFWB).²² Despite these promising findings, WFWB is currently restricted to military operations and therefore the data cannot be fully extrapolated to civilian practice. Our analysis used similar techniques by assessing our institutional WB:RBC, which uses cold-stored WB, and demonstrated significant 4 and 24-hour mortality improvements within the high ratio WB:RBC cohorts at each time period assessed.²² These findings reveal that higher ratios of WB may offer an early mortality benefit, particularly hemorrhage-related mortality, within civilian trauma patients.^{23 24}

In a single-center observational study, Brill *et al* were the first to prospectively demonstrate that WB was independently associated with a 4.1-fold increased 30-day survival and a 60% reduction in 24-hour transfusion requirements for traumatically injured

Table 4 Multivariable logistic regression analysis assessing 4 and 24 h mortality

Variable	1 h		2 h		3 h		24 h	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
WB:RBC \geq 1	0.165 (0.04 to 0.70)	0.015	0.265 (0.09 to 0.78)	0.015	0.186 (0.05 to 0.76)	0.019	0.151 (0.05 to 0.53)	0.003
Penetrating	0.317 (0.73 to 6.5)	0.161	0.997 (0.77 to 4.77)	0.199	2.135 (0.72 to 6.35)	0.173	1.879 (0.72 to 4.90)	0.197
HR	0.970 (0.95 to 0.99)	0.001	0.977 (0.96 to 0.99)	0.004	0.970 (0.95 to 0.99)	0.001	0.978 (0.96 to 0.99)	0.006
SBP	1.007 (0.99 to 1.02)	0.415	1.000 (0.99 to 1.02)	0.949	1.007 (0.99 to 1.02)	0.425	1.000 (0.99 to 1.02)	0.975
ISS	0.993 (0.94 to 1.05)	0.790	1.001 (0.96 to 1.05)	0.959	0.997 (0.95 to 1.05)	0.923	1.001 (0.96 to 1.05)	0.963
GCS	0.925 (0.83 to 1.03)	0.146	0.915 (0.84 to 1.00)	0.054	0.937 (0.84 to 1.04)	0.224	0.921 (0.84 to 1.01)	0.080
Lactate	1.158 (1.06 to 1.27)	0.002	1.189 (1.10 to 1.29)	<0.01	1.151 (1.05 to 1.26)	0.002	1.191 (1.10 to 1.30)	<0.01

GCS, Glasgow Coma Scale; HR, heart rate; ISS, Injury Severity Score; SBP, systolic blood pressure; WB:RBC, whole blood to packed red blood cell ratio.

Table 5 Average 24 h blood product requirements

Average product requirements	WB:RBC $>$ 1	WB:RBC $<$ 1	P value
1 h			
WB	4.4	0.7	<0.01
RBC	1.8	5.1	<0.01
FFP	1.8	4.7	<0.01
PLT	0.1	0.4	<0.01
Total units	8.0	10.9	<0.01
2 h			
WB	5.4	1.1	<0.01
RBC	2.2	7.9	<0.01
FFP	2.3	7.1	<0.01
PLT	0.2	0.4	<0.01
Total units	9.9	16.1	<0.01
3 h			
WB	5.5	1.2	<0.01
RBC	2.4	9.2	<0.01
FFP	2.5	8.3	<0.01
PLT	0.2	0.5	<0.01
Total units	10.7	19.7	<0.01
24 h			
WB	5.7	1.7	<0.01
RBC	2.8	11	<0.01
FFP	3.2	10.1	<0.01
PLT	0.5	1.7	<0.01
Total units	12.1	24.4	<0.01

FFP, fresh frozen plasma; PLT, platelets; WB:RBC, whole blood to packed red blood cell ratio.

patients.¹⁴ Hazelton *et al* subsequently demonstrated a 48% reduction in mortality at 24 hours and 9% reduction in bleeding complications when WB was incorporated into a civilian MTP in the first prospective multicenter trial assessing WB.¹³ Current recommendations, however, suggest that mortality outcomes in patients with hemorrhagic shock should be evaluated between 3 and 6 hours from arrival to coincide with the physiology of hemorrhage-related deaths and mitigate the risk of later causes of mortality.^{13 14 24} In accordance with these recommendations, Sperry *et al* demonstrated that WB was independently associated with a decreased 4-hour mortality in patients who displayed an increased prehospital probability of death (RR 0.52, p=0.01).¹⁵ Similarly, Torres *et al* recently demonstrated an early improvement in survival associated with WB use during massive transfusions in a large nationwide retrospective study.²⁵

Our analysis builds on these studies by assessing the WB:RBC patients received. We intentionally chose to assess this ratio as patients most frequently receive a combination of both WB and blood components at our institution. Furthermore, we think that it remains likely that certain patient populations may experience a greater benefit from WB than others. Due to this, our analysis sought to target those who we thought would be at greatest risk for death secondary to hemorrhage. As such, we intentionally chose to exclude patients with TBI in efforts to mitigate risk of competing mortality bias and more clearly assess the role of WB in pure hemorrhagic shock. Our data differ from previous studies in that we aimed to assess how patients received WB during their resuscitation as we thought this distinction (ie, the rate and frequency compared with other blood components) likely plays a critical role during the resuscitative period. We

thought our findings support this notion and continue to expand on the growing body of literature surrounding WB.

Beyond the mortality benefit displayed within our high ratio cohort, the decreased overall transfusion requirements within this group represent a clinically important finding.²⁶ We hypothesize that the lower transfusion requirements within the high ratio cohort suggest that higher ratios of WB may aid in promoting hemostasis, preventing vasoplegia, and mitigating trauma-induced coagulopathy, although this study was not designed to study these factors.

While this study represents the first civilian study to assess how WB is transfused compared with other blood components, it is not without its limitations. The retrospective nature of this study places our data at risk for multiple biases and should only be viewed as hypothesis generating. Our data were limited to variables collected within our institutional database and, as with any observational study, are at risk for unknown, uncollected, and unmeasured confounders. Specifically, our data did not analyze time to hemorrhage control or surgical procedures performed; both of which we recognize as critically important aspects in the care of trauma patients. Moreover, this study only encompasses patients from a single institution. While this may offer some benefit by mitigating variable treatment across multiple centers, our findings may not be applicable to other institutions or trauma systems, especially those with different resuscitation protocols. We used anatomic and physiologic surrogates to represent the degree of presenting illness, which should be taken into account as direct injury patterns and specific surgical procedures performed were not available for this analysis. Despite these limitations, we think that our findings add to the current body of literature surrounding WB and its use in civilian trauma. The independent association with decreased mortality and transfusion requirements displayed within high WB:RBC cohort provides initial data toward optimizing WB transfusion practices. Although, the limitations within our current study support the need for future prospective randomized controlled trials assessing WB transfusions in civilian trauma. Toward this, two trials examining prehospital WB (NCT04684719) and in-hospital WB (NCT05638581) are currently enrolling patients and should provide definitive evidence surrounding WB use in hemorrhagic shock.

CONCLUSION

In conclusion, this retrospective analysis demonstrated that preferentially transfusing WB compared with a balanced blood component transfusion strategy during the early resuscitative periods, as evidenced by a high WB:RBC, was associated with decreased 4 and 24-hour mortality and decreased transfusion requirements in severely injured patients at risk for death secondary to hemorrhage. We hope that these findings will help to propel further analyses and act as a stepping stone to subsequent studies assessing the optimal incorporation of WB into civilian transfusion practices. Further high-level prospective studies should be sought to appropriately define the role of WB for trauma patients in hemorrhagic shock.

Contributors DL, PH, RDB, ZH, JOJ, and JBH developed the idea for this study. DL, OR, and EWB conducted the literature search. DL, PH, OR, RDB and ZH contributed to study design. DL, PH, RDB, and EWB participated in data acquisition. DL, PH, OR, RDB, ZH, JDK, JOJ, and JBH contributed to data analysis and interpretation. DL, OR, RDB, and EWB drafted the article. PH, ZH, JDK, JOJ, and JBH critically revised the final article. All authors reviewed and approved the final article. DL is responsible for the overall content of the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Local institutional review board approval was obtained before data abstraction and analysis.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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