High whole blood to total transfusion volume ratio and survival outcomes in patients with trauma requiring massive transfusions

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ABSTRACT

Objective Whole blood (WB) resuscitation has been reported to improve haemostasis and reduce mortality in trauma patients with severe haemorrhage. However, the ideal ratio of WB to total transfusion volume (TTV) and whether a high WB to TTV ratio is associated with favourable clinical outcomes for patients with trauma requiring massive transfusion remains unclear. We aimed to investigate the effectiveness of a high WB to TTV ratio in the treatment of patients with trauma requiring massive transfusion and explore the nonlinear relationship between the ratio of WB to TTV and patient's outcomes.

Methodology We performed a retrospective cohort study using the National Trauma Data Bank from the USA in 2020. The study included patients aged ≥16 years who received WB transfusion within 4 hours of hospital arrival. Patients were categorised into two groups based on the optimal cut-off value (0.5) of the WB to TTV ratio. The primary outcomes were in-hospital mortality at 24 hours and 30 days. Secondary outcomes included transfusion-related adverse events.

Results Among the 902 patients (median (IQR) age, 34 (24–51) years; 783 male (86.9%)), the optimal cut-off value for the WB to TTV ratio was 0.5. Based on this cut-off value, 143 patients (15.85%) were classified into the high WB group and 759 (84.15%) into the low WB group. Inverse probability of treatment weighting-adjusted logistic regression demonstrated that the high WB group had lower odds of 24-hour mortality (OR, 0.29; 95% CI 0.22 to 0.38; p<0.001) and 30-day mortality (OR, 0.40; 95% CI 0.32 to 0.49; p<0.001) compared with the low WB group.

Conclusion A high WB to TTV ratio was associated with reduced mortality in patients with trauma requiring massive transfusion. These findings suggested that incorporating a high WB to TTV ratio into resuscitation protocols may improve outcomes for patients with trauma, warranting further research to optimise transfusion strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Whole blood (WB) improves haemostasis and reduces mortality in trauma-related severe haemorrhage, yet the optimal WB-to-total transfusion volume (TTV) ratio for patients with trauma needing massive transfusion remains unclear.

WHAT THIS STUDY ADDS

⇒ For patients with trauma requiring massive transfusion, a WB/TTV ratio ≥0.5 (optimal cut-off) was linked to lower 24 hour (OR 0.29) and 30-day mortality (OR 0.40).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlighted the potential of a high WB/TTV ratio to improve outcomes, supporting its integration into resuscitation protocols and prompting further research to optimise transfusion strategies, with possible implications for clinical guidelines.

INTRODUCTION

Trauma remains one of the leading causes of death in the USA,[1] with haemorrhage accounting for the majority of potentially preventable post-trauma deaths.[2–4] Current damage control resuscitation strategies emphasise the importance of a balanced transfusion approach, utilising either separated blood components or whole blood (WB) to address trauma-induced coagulopathy.[5] The use of WB, initially adopted in military settings, is now being integrated into civilian medical practice.[6 7] Studies have shown that WB resuscitation improves haemostasis and reduces mortality in patients with trauma with severe haemorrhage.[8–13] However, due to limited WB inventory at trauma centres, patients requiring massive transfusion often receive a combination of WB and component transfusions during resuscitation. Recent evidence has indicated that early administration of WB as part of a massive transfusion protocol was associated with a 60% reduction in 24-hour in-hospital mortality and a 68% reduction in 30-day mortality, compared with late administration.[9]

The optimal transfusion ratio of WB for patients with trauma remains uncertain. Further studies have explored the relationship between the WB to total transfusion volume (TTV) ratio and mortality in adult patients with trauma. Aoki *et al*[14] categorised patients into quartiles based on their WB ratio and reported that the highest WB ratio quartile was associated with reduced 24-hour mortality compared with the lowest quartile. Similarly, Gallastegi *et al*[15] demonstrated that high WB to TTV ratios were correlated with improved survival outcomes. Specifically, each 10% increase in the WB

to TTV ratio resulted in a 15% reduction in 24-hour mortality. These findings suggested that higher WB ratios may improve survival outcomes in patients with trauma. Previous studies have predominantly relied on receiver operating characteristic (ROC) curves or IQRs to determine thresholds. However, it is worth noting that these methods depend on present thresholds or forcibly discretise continuous variables, which may fail to capture the true characteristics of the data. In contrast, restricted cubic spline (RCS) offers the flexibility to fit non-linear relationships without relying on predefined functional forms, enabling the exploration of complex associations between continuous variables and outcomes.[16] The objective of this study was to evaluate the association between WB to TTV ratio and mortality in patients requiring massive transfusion via RCS. We investigated whether a non-linear relationship exists between this transfusion ratio and survival to determine the optimal transfusion strategy.

STUDY DESIGN AND METHODS

Data sources

This cohort study was a retrospective analysis of the National Trauma Data Bank (NTDB), a nationwide, multicentre, prospective and observational trauma registry spanning from 1 January 2020 to 31 December 2020. NTDB is the world's largest repository of trauma-related clinical data, containing over 7.5 million electronic records from more than 900 trauma centres across the USA.[17] The requirement for informed consent was waived due to the use of anonymised patient data. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[18]

Inclusion and exclusion criteria

Eligible participants were adults aged 16 years or older admitted to level I or II trauma centres and requiring massive transfusion (defined as more than 5 units of red blood cells (RBCs) or WB within the first 4 hours of emergency department (ED) admission).[19 20] We excluded patients with no signs of life at arrival, those who died in the ED within 24 hours, patients with burns, those with missing transfusion data, those transferred to another facility and those who died within 60 min after arrival.

Exposure

Patients were divided into two groups based on different identified WB to TTV ratios. The WB:TTV ratio was calculated by dividing the volume of WB transfused by the TTV, which included the sum of WB, RBC, FFP and platelet (PLT) transfusion volumes. For the calculation of the WB:TTV ratio and patient population selection, the standard unit volumes for blood products were defined as follows: WB, 500 mL; RBC, 300 mL; FFP, 250 mL; and PLT, 50 mL.[15 21 22]

Outcomes

The primary outcomes were 24-hour in-hospital mortality and 30-day in-hospital mortality. Secondary outcomes, selected a priori, included transfusion-related adverse events, such as overall adverse events, pulmonary embolism (PE), deep vein thrombosis (DVT), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and sepsis.

Statistical analysis

Data analysis was conducted from 1 November 2024 to 8 January 2025. Continuous variables were described as medians and IQRs, while categorical variables were summarised as numbers and percentages (%). Multiple imputations were performed to address missing data assumed to be missing at random. The missing rates of variables are detailed in online supplemental eTable 1.

RCS with three knots, based on Akaike information criterion (AIC), was used to explore the potential non-linear relationship between the WB to TTV ratio (as a continuous variable) and in-hospital mortality in order to determine the optimal cut-off value for the WB to TTV ratio. Analyses were adjusted for potential confounders, including patient characteristics (age, sex, race, body mass index) and comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease and cerebrovascular accident, injury characteristics (mechanism of injury (blunt or penetrating), injury severity score (ISS), ED vital signs (systolic blood pressure, heart rate and respiratory rate), Glasgow Coma Scale score and haemorrhage control surgeries (laparotomy, thoracotomy, sternotomy, extremity amputation and traumatic amputation)) and hospital characteristics (ACS trauma centre verification level (level I and level II)).

Inverse probability of treatment weighting (IPTW) was applied using propensity scores derived from a logistic regression model, with the WB group as the dependent variable and all measured covariates as independent variables. The standardised mean difference (SMD) was used to assess balance between groups, with $|SMD|>0.1$ indicating imbalance. After IPTW, logistic regression models adjusted for any unbalanced confounders were used to evaluate the associations between the WB ratio and primary and secondary outcomes. Results were reported as ORs with 95% CIs. All analyses were performed using R software, V.4.41 (R Studio).

Subgroup analysis

To further examine the heterogeneity of trauma-induced coagulopathy within the study population, we conducted a subgroup analysis focusing on specific patient clusters. The subgroups included patients with blunt injury mechanism, penetrating injury mechanism, Abbreviated Injury Scale (AIS) body region 1 (head) >3, AIS body region 4 (thorax) >3 and AIS body region 5 (abdominal and pelvic contents) >3. Similar to the primary analysis, we applied IPTW to control for confounding variables in these subgroups. Additionally, non-linear spline curves were generated to explore potential non-linear relationships between WB:TTV ratio and clinical outcomes.

Sensitivity analysis

As for sensitivity analyses, we conducted three additional analyses to verify the robustness of our findings. First, we performed unadjusted logistic regression models (model 1), adjusted logistic regression models for potential confounders (model 2) and adjusted logistic regression models using complete case data (model 3). Additionally, to address potential bias from unmeasured confounding factors, the E-value was computed to enhance the robustness of our findings.[23 24] The E-value represents the minimum strength of association required between an unmeasured confounder and both the outcome and exposure variables to fully explain the observed treatment–outcome relationship.

RESULTS

RCS for outcomes

A flowchart of the study is shown in figure 1. A total of 902 patients (median (IQR) age, 34 (24–51) years; 783 males (86.9%); 118 females (13.1%)) were included in the analysis (table 1). RCS analysis identified an optimal cut-off value of 0.5 for the WB:TTV ratio (figure 2A–F). Furthermore,

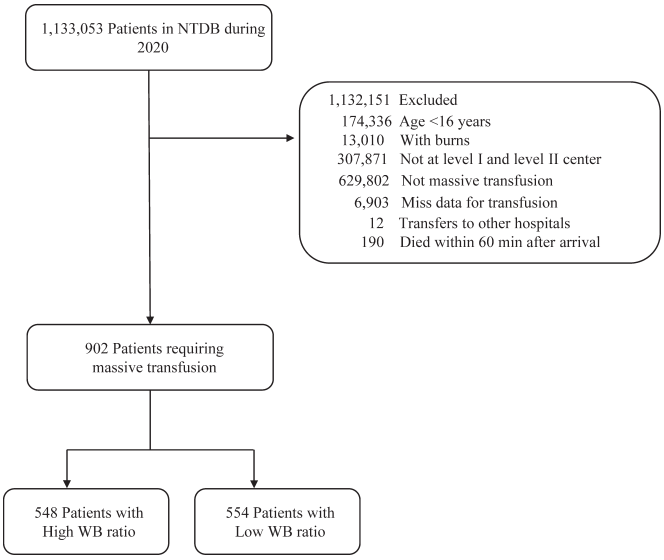

Figure 1 Study flowchart. WB, whole blood.

to investigate model robustness, we revealed that the non-linear models exhibited lower AIC and BIC values than their linear counterparts, although the p value equals 0.138 (online supplemental eTable 2). A notable trend was observed in the relationship between the WB:TTV ratio and 24-hour mortality. As the WB to TTV ratio approached 0, the OR was approximately 2. However, as the ratio increased, the OR decreased rapidly. The curve intersected the reference line (OR=1) at a ratio of 0.2–0.3, indicating that beyond this threshold, mortality rates decreased. As the ratio continued to increase, the OR gradually declined and stabilised at ratios exceeding 0.5 (figure 2A–F), suggesting an 'upper limit effect'. Subgroup analyses demonstrated consistent trends with those observed in the overall population, as illustrated by the RCS curves.

Patient characteristics and treatment details

The study population was stratified into two groups based on the WB to TTV ratio: a high WB group (ratio >0.5) and a low WB group (ratio ≤0.5). Patient characteristics are summarised in table 1. The median (IQR) ISS score was 29 (21–41). Treatment details, adverse events and outcomes are presented in table 2. The median (IQR) transfusion volumes within 4 hours were as follows: in the high WB group, 0 (0–3) units of RBC, 0 (0–3) units of FFP and 0 (0–4) units of PLT; in the low WB group, 11 (7–19) units of RBC, 8 (5–15) units of FFP and 6 (4–12) units of PLT. The 24-hour mortality rates were 9.79% (14/143) in the high WB group and 24.1% (183/759) in the low WB group.

Table 1 Patient characteristics of the study cohort

	All patients	Low WB	High WB	P value	SMD (95% CI)	Weighted SMD
Number of patients	N=902	N=759	N=143			
Demographics						
Age, median (IQR), years	34.0 (24.0, 51.0)	33.0 (24.0, 51.0)	38.0 (27.0, 54.0)	0.017	−0.18 (−0.36 to −0.00)	0.014
Race, n (%)				0.280	0.00 (−0.02 to 0.02)	<−0.001
Asian	13 (1.54)	11 (1.54)	2 (1.53)			
Black	301 (35.6)	256 (35.8)	45 (34.4)			
White	428 (50.6)	362 (50.6)	66 (50.4)			
American Indian	6 (0.71)	3 (0.42)	3 (2.29)			
Other	98 (11.6)	83 (11.6)	15 (11.5)			
BMI, median (IQR)	27.5 (24.1, 31.9)	27.2 (24.0, 31.6)	29.0 (24.7, 32.7)	0.076	−0.11 (−0.29 to 0.07)	−0.019
Sex, n (%)				0.547	−0.02 (−0.08 to 0.03)	0.001
Male	783 (86.9)	656 (86.5)	127 (88.8)			
Female	118 (13.1)	102 (13.5)	16 (11.2)			
ED vital signs, median (IQR)						
SBP, mm Hg	96.0 (80.0, 121)	93.0 (78.0, 120)	102 (85.0, 130)	0.003	−0.29 (−0.47 to −0.11)	0.021
HR, beats/min	117 (97.0, 134)	118 (97.8, 134)	114 (90.0, 133)	0.130	0.16 (−0.02 to 0.34)	0.022
RR, beats/min	22.0 (18.0, 27.0)	22.0 (18.0, 28.0)	20.0 (18.0, 25.0)	0.133	0.11 (−0.07 to 0.29)	−0.066
Glasgow Coma Scale score, median (IQR)	11.0 (3.00, 15.0)	11.0 (3.00, 15.0)	11.0 (3.00, 15.0)	0.860	0.01 (−0.17 to 0.19)	−0.021
Mechanism of injury, n (%)				0.082	−0.08 (−0.17 to 0.00)	−0.018
Blunt	473 (52.4)	388 (51.1)	85 (59.4)			
Penetrating	429 (47.6)	371 (48.9)	58 (40.6)			
ISS, median (IQR)	29.0 (21.0, 41.0)	29.0 (22.0, 41.0)	26.0 (17.0, 38.0)	0.005	0.25 (0.07 to 0.42)	0.049
Comorbidities, n (%)						
Hypertension	112 (12.4)	89 (11.7)	23 (16.1)	0.190	0.04 (−0.02 to 0.11)	0.002
Diabetes	45 (4.99)	39 (5.14)	6 (4.20)	0.791	−0.01 (−0.05 to 0.03)	−0.007
COPD	18 (2.00)	11 (1.45)	7 (4.90)	0.015	0.03 (−0.00 to 0.07)	−0.002
CVA	2 (0.22)	2 (0.26)	0 (0.00)	1.000	−0.00 (−0.01 to 0.00)	0.000
ACS trauma centre, n (%)				0.763	0.01 (−0.04 to 0.06)	0.002
Level I	841 (93.2)	709 (93.4)	132 (92.3)			
Level II	61 (6.76)	50 (6.59)	11 (7.69)			

ACS, American College of Surgeons; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ED, emergency department; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; RR, respiratory rate; SBP, systolic blood pressure; SMD, standardised mean difference; WB, whole blood.

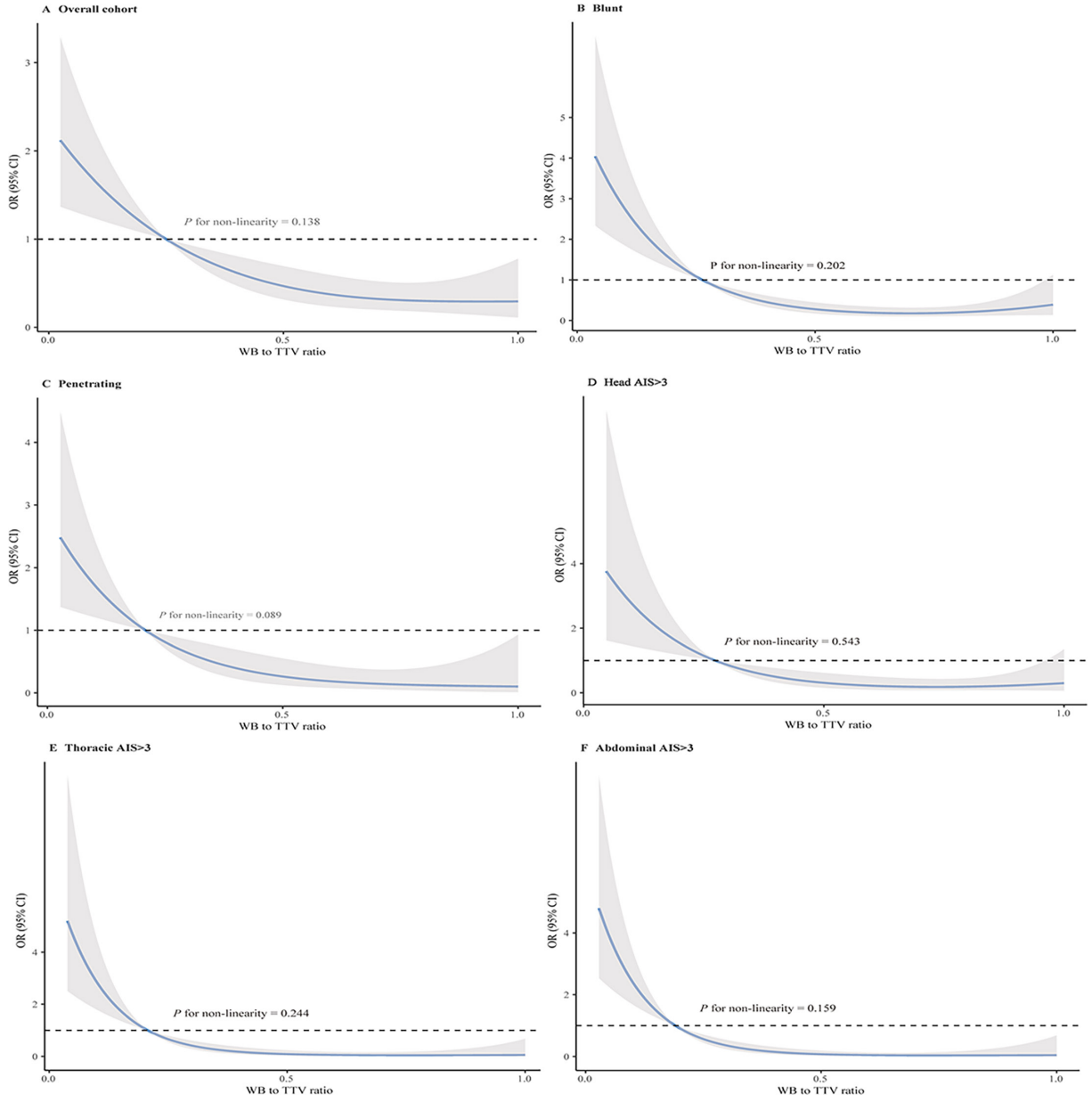

Figure 2 Restricted cubic spline for whole blood (WB) to total transfusion volume (TTV) ratio in overall cohort and in each subgroup. Association between the WB to TTV ratio and in-hospital mortality in the overall cohort (A) and in each subgroup (B–F). The model was fitted with a restricted cubic spline of the WB to TTV ratio adjusted for age, sex, race, body mass index, comorbidities, mechanism of injury, injury severity score, emergency department (ED) vital signs, Glasgow Coma Scale score, haemorrhage control surgeries and hospital characteristics. Each subgroup is defined as follows: (B) blunt injury, (C) penetrating injury, (D) head Abbreviated Injury Scale (AIS) >3, (E) thoracic AIS >3, (F) abdominal AIS >3.

Similarly, the 30-day mortality rates were 20.3% (29/143) in the high WB group and 36.0% (273/759) in the low WB group.

Logistic regression model

The propensity score distributions of the high WB group and low WB group overlapped (online supplemental eFigure 1). In the primary analysis, compared with the low WB group, the OR of IPTW for the high WB group was 0.29 (95% CI 0.22 to 0.38; p<0.001) for 24-hour mortality and 0.40 (95% CI 0.32 to 0.49; p<0.001) for 30-day mortality (table 3). Results of secondary outcomes are also presented in table 3. The incidence of AKI (OR: 0.35 (95% CI 0.23 to 0.52); p<0.001) was lower in the high WB group compared with the low WB group, while PE (OR: 1.81 (95% CI 1.23 to 2.66); p=0.003), DVT (OR: 2.75 (95% CI 1.96 to 3.85); p<0.001) and ARDS (OR: 2.63 (95% CI 1.46 to 4.75); p=0.001) were higher. However, no statistically significant differences were observed in the incidence of sepsis.

Subgroup analysis

In subgroup analyses, after adjusting for factors such as injury mechanisms and injury sites, the high WB group consistently demonstrated a favourable survival prognosis: for 24-hour mortality, blunt injury (OR: 0.26 (95% CI 0.18 to 0.39); p<0.001), penetrating injury (OR: 0.27 (95% CI 0.17 to 0.42); p<0.001), head AIS >3 (OR: 0.09 (95% CI 0.04 to 0.20); p<0.001), thoracic AIS >3 (OR: 0.18 (95% CI 0.10 to 0.33); p<0.001) and abdominal AIS >3 (OR: 0.23 (95% CI 0.14 to 0.36); p<0.001) (figure 3). For 30-day mortality, blunt injury (OR: 0.42 (95% CI 0.31 to 0.55); p<0.001), penetrating injury (OR: 0.29 (95% CI 0.20 to 0.42); p<0.001), head AIS >3 (OR:

Table 2 Treatment details, adverse events and outcomes

Parameter	Lower WB	High WB	P value
Transfusion within 4 hours, median (IQR), unit			
RBC	11.0 (7.00, 19.0)	0.00 (0.00, 3.00)	<0.001
FFP	8.00 (5.00, 15.0)	0.00 (0.00, 3.00)	<0.001
PLT	6.00 (4.00, 12.0)	0.00 (0.00, 4.00)	<0.001
Intervention for haemorrhage control within 4 hours	628 (84.8)	97 (69.8)	<0.001
Adverse event, n (%)			
PE	38 (5.01)	12 (8.39)	0.155
DVT	45 (5.93)	22 (15.4)	<0.001
ARDS	13 (1.71)	6 (4.20)	0.102
AKI	80 (10.5)	7 (4.90)	0.052
Sepsis	41 (5.40)	5 (3.50)	0.458
In-hospital mortality, n (%)			
24 hours	183 (24.1)	14 (9.79)	<0.001
30 days	273 (36.0)	29 (20.3)	<0.001

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; FFP, fresh frozen plasma; LOS, length of stay; PE, pulmonary embolism; PLT, platelet; RBC, red blood cell; WB, whole blood.

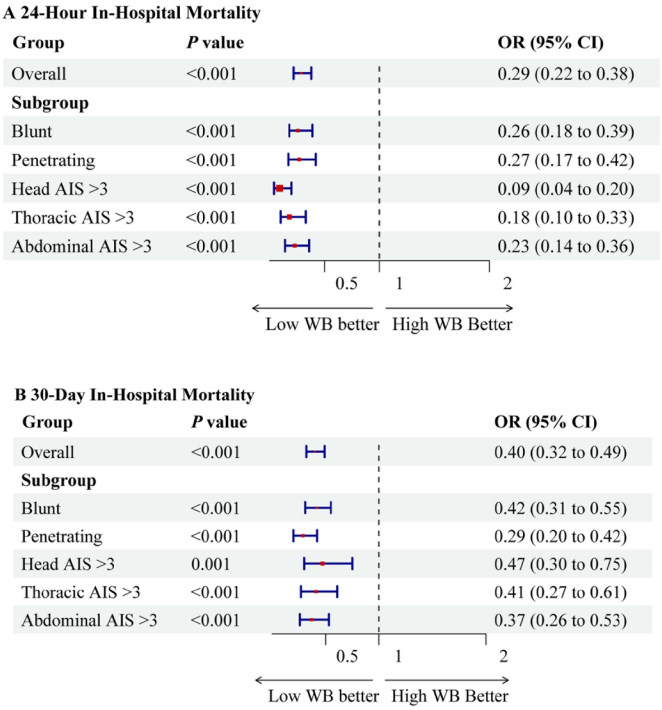

Figure 3 Forest plot of ORs and 95% CIs of 24-hour (A) and 30-day (B) in-hospital mortality for main and subgroup analysis. AIS, Abbreviated Injury Scale; WB, whole blood.

0.47 (95% CI 0.30 to 0.75); p<0.001), thoracic AIS >3 (OR: 0.41 (95% CI 0.27 to 0.61); p<0.001) and abdominal AIS >3 (OR: 0.37 (95% CI 0.26 to 0.53); p<0.001). However, the rate of adverse events remained elevated (see online supplemental eTables 3–7).

Sensitivity analysis

The results of the sensitivity analysis are summarised in online supplemental eTable 2. In the unadjusted logistic regression model (model 1), logistic regression model adjusting for potential confounders (model 2) and logistic regression model adjusting for potential confounders using all data with complete cases (model 3), the ORs for 24-hour mortality were 0.35 (0.19 to 0.59), 0.19 (0.04 to 0.60) and 0.30 (0.16 to 0.56), respectively. Results for 30-day mortality were similar.

In the multivariable logistic regression analysis for 24-hour in-hospital mortality, the E-value for the OR was 6.35. This implies that an unmeasured confounder, which was associated with both the treatment and the outcome, might potentially explain the observed association. Given the measured confounders, the OR of each such association (between the unmeasured confounder and either the treatment or the outcome) would need to be at least 6.35. Similarly, the E-value for 30-day in-hospital mortality was 4.44, further supporting the robustness of the findings. The E-values for adverse outcomes also showed consistent results, as detailed in online supplemental eTable 8.

Table 3 Results of logistic regression analysis weighted by IPTW for each outcome in the overall cohort

	OR (95% CI)	P value
Primary		
24 hours in-hospital mortality	0.29 (0.22 to 0.38)	<0.001
30 days in-hospital mortality	0.40 (0.32 to 0.49)	<0.001
Secondary		
Overall adverse event	1.42 (1.14 to 1.77)	0.002
PE	1.81 (1.23 to 2.66)	0.003
DVT	2.75 (1.96 to 3.85)	<0.001
ARDS	2.63 (1.46 to 4.75)	0.001
AKI	0.35 (0.23 to 0.52)	<0.001
Sepsis	1.01 (0.67 to 1.52)	0.954

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; IPTW, inverse probability of treatment weights; PE, pulmonary embolism.

DISCUSSION

On the whole, based on the identified WB/TTV threshold (0.5), we observed an inverse relationship between threshold elevation and OR values, indicating reduced mortality rates. Notably, however, a plateau effect emerged when thresholds exceeded 2, precluding observation of survival benefits. This indicated the existence of an optimal WB/TTV ratio that maximised clinical benefits for patients with trauma. Subgroup analyses revealed that the relationship between the WB to TTV ratio and mortality was relatively consistent across different injury populations.

In a study by Gallastegi *et al*,[15] investigating the interaction between WB and component-based resuscitation, it was found that a higher ratio of WB to blood components was associated with lower mortality, which aligned with the findings of our study. The authors utilised fractional polynomial models to illustrate the relationship between different WB to TTV ratios and 4-hour mortality. The optimal cut-off value for the WB to blood component ratio was determined using the point on the ROC curve that maximised predictive accuracy.[25] This differed from our study, in which we employed RCS to explore the potential non-linear relationship between the WB to TTV ratio as a continuous variable and in-hospital mortality. This approach allowed for greater flexibility in capturing complex relationships between variables, avoiding potential issues of overfitting or underfitting that may arise with fractional polynomial models.[26–28] The RCS method does not require prespecification of a functional form, enabling a more accurate reflection of the

true distribution of the data and thereby providing more reliable statistical inferences. Moreover, RCS can integrate with multivariable regression to control confounders. In contrast, although the method of determining the optimal cut-off value using the ROC curve is intuitive, it may lose some information inherent in continuous variables. Additionally, the determination of the cut-off value is sample dependent, which may limit the generalisability of the results. Therefore, our research approach not only better aligns with the actual characteristics of the data but also offers more precise and comprehensive reference evidence for clinical decision-making.

In an observational study involving 1051 patients with haemorrhagic shock, Sperry *et al*[29] found that the ratio of WB to total blood components was an independent predictor of 29-day survival. As the proportion of WB increased, the independent risk of mortality consistently decreased. Feeney[30] *et al* found that, in a paediatric level I trauma centre, an increase in the proportion of WB in total blood product resuscitation was independently associated with improved survival in injured children. For every 38% increase in the proportion of WB in the TTV, in-hospital mortality decreased by 0.001%. In a study evaluating the dose-dependent effects of WB on the outcomes of civilian patients with trauma with haemorrhagic shock, Hosseinpour *et al*[31] found that a higher ratio of WB to RBC was associated with improved early and late mortality in patients with trauma with haemorrhagic shock. A study on the use of WB in military settings found that patients who received a higher ratio of WB to RBCs had lower mortality rates.[32] Similarly, in a study by Aoki *et al*,[14] patients were divided into four groups based on quartiles of the WB to RBC ratio to investigate the association between this ratio and mortality risk in patients with trauma. The study found that patient mortality consistently decreased as the WB to RBC ratio increased. The survival benefits associated with a higher ratio of WB further corroborate the findings of our study.

Previous studies[13] have suggested that the mechanisms by which the use of WB may improve outcomes in trauma populations include providing higher concentrations of clotting factors, superior haemostatic properties, reduced overall blood volume and preservative use, and amelioration of trauma-induced endothelial dysfunction. Compared with equivalent units of component blood products, WB contains higher concentrations of RBCs, plasma proteins, fibrinogen and PLTs. Haemorrhagic shock and trauma can induce endothelial barrier damage, inflammation and coagulopathy. Previous studies[33 34] have found that in murine models of haemorrhagic shock, resuscitation with WB attenuate systemic inflammation and organ injury. Baucom[35] *et al* found that resuscitation with WB following haemorrhagic shock reduced endothelial syndecan-1 shedding and mitigated lung injury.

Regarding transfusion-related adverse events, our study revealed no differences between the two groups in terms of PE, DVT or ARDS. However, the high WB group demonstrated a protective effect against AKI and sepsis, which aligned with findings from previous studies.[14 36–38] A study by Aoki[15] *et al* demonstrated that a higher ratio of WB was associated with a lower incidence of AKI (OR: 0.71, 95% CI 0.63 to 0.80). Similarly, research by Hanna[38] *et al* indicated that in the resuscitation of severely injured civilian patients with trauma, the use of WB as an adjunct to component therapy was linked to a reduction in major complications, including AKI and sepsis.

Strengths and limitations

The findings of this study have the potential to help determine the optimal transfusion ratio for severely injured patients with trauma in clinical settings. However, our study also has several limitations. First, due to the constraints of the NTDB, certain covariates such as tranexamic acid could not be obtained from the database. Second, although we attempted to control for potential confounding biases using the IPTW method, there may still be some unmeasured confounders. Third, missing variables could impact the results of this study, although multiple imputations and sensitivity analyses were conducted, confirming that the study's findings remained unchanged. Fourth, the retrospective and observational design precludes us from establishing a causal relationship between the WB ratio and mortality. Future multicentre prospective randomised studies are necessary. Finally, our study included a high proportion of male patients (90%), which was not due to gender-specific inclusion criteria but consistent with prior trauma studies using the NTDB, reflecting the real-world demographic pattern of trauma populations. However, this may limit the generalisability of our findings to female patients with trauma, which may warrant further gender-specific research.

CONCLUSIONS

This multicentre study suggested that the use of higher ratio of WB to TTV was associated with lower mortality in patients with trauma requiring massive blood transfusion. Nonetheless, when the ratio exceeds 0.5, a ceiling effect might occur. It is necessary to conduct future randomised controlled trials centred on patients to verify the effectiveness of high WB ratios in trauma situations.

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Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available in a public, open access repository. Publicly available datasets were analysed in this study. These data can be found in https://www.facs.org/quality-programs/trauma/quality/national-trauma-data-bank/datasets/.

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REFERENCES

1 Ahmad FB, Cisewski JA, Anderson RN. Mortality in the United States — Provisional Data, 2023. *MMWR Morb Mortal Wkly Rep* 2023;73:677–81.
2 Holcomb JB, Moore EE, Sperry JL, *et al*. Evidence-Based and Clinically Relevant Outcomes for Hemorrhage Control Trauma Trials. *Ann Surg* 2021;273:395–401.

3 Eastridge BJ, Holcomb JB, Shackelford S. Outcomes of traumatic hemorrhagic shock and the epidemiology of preventable death from injury. *Transfusion* 2019;59:1423–8.
4 Davis JS, Satahoo SS, Butler FK, *et al*. An analysis of prehospital deaths: Who can we save? *J Trauma Acute Care Surg* 2014;77:213–8.
5 Holcomb JB, Jenkins D, Rhee P, *et al*. Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma. *J Trauma Acute Care Surg* 2007;62:307–10.
6 Spinella PC. Warm fresh whole blood transfusion for severe hemorrhage: U.S. military and potential civilian applications. *Crit Care Med* 2008;36:S340–5.
7 Apelseth TO, Strandenes G, Kristoffersen EK, *et al*. How do I implement a whole blood–based blood preparedness program in a small rural hospital? *Transfusion* 2020;60:2793–800.
8 Feinberg GJ, Tillman AC, Paiva ML, *et al*. Maintaining a whole blood-centered transfusion improves survival in hemorrhagic resuscitation. *J Trauma Acute Care Surg* 2024;96:749–56.
9 Torres CM, Kenzik KM, Saillant NN, *et al*. Timing to First Whole Blood Transfusion and Survival Following Severe Hemorrhage in Trauma Patients. *JAMA Surg* 2024;159:374–81.
10 Meizoso JP, Cotton BA, Lawless RA, *et al*. Whole blood resuscitation for injured patients requiring transfusion: A systematic review, meta-analysis, and practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg* 2024;97:460–70.
11 Aoki M, Katsura M, Matsushima K. Association Between Whole Blood Transfusion and Mortality Among Injured Pediatric Patients. *Ann Surg* 2024;279:880–4.
12 Brill JB, Tang B, Hatton G, *et al*. Impact of Incorporating Whole Blood into Hemorrhagic Shock Resuscitation: Analysis of 1,377 Consecutive Trauma Patients Receiving Emergency-Release Uncrossmatched Blood Products. *J Am Coll Surg* 2022;234:408–18.
13 Hazelton JP, Ssentongo AE, Oh JS, *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;276:579–88.
14 Aoki M, Abe T, Komori A, *et al*. Association between whole blood ratio and risk of mortality in massively transfused trauma patients: retrospective cohort study. *Crit Care* 2024;28:253.
15 Dorken-Gallastegi A, Spinella PC, Neal MD, *et al*. Whole Blood and Blood Component Resuscitation in Trauma: Interaction and Association With Mortality. *Ann Surg* 2024;280:1014–20.
16 Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. *Bone Marrow Transplant* 2020;55:675–80.
17 Hashmi ZG, Kaji AH, Nathens AB. Practical Guide to Surgical Data Sets: National Trauma Data Bank (NTDB). *JAMA Surg* 2018;153:852–3.
18 von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.
19 Lin VS, Sun E, Yau S, *et al*. Definitions of massive transfusion in adults with critical bleeding: a systematic review. *Crit Care* 2023;27:265.
20 Green L, Tan J, Grist C, *et al*. Aetiology and outcome of massive transfusion in two large London teaching hospitals over a 3-year period (2012–2014). *Transfus Med* 2017;27:342–7.
21 Dorken Gallastegi A, Naar L, Gaitanidis A, *et al*. Do not forget the platelets: The independent impact of red blood cell to platelet ratio on mortality in massively transfused trauma patients. *J Trauma Acute Care Surg* 2022;93:21–9.
22 World Health Organization. Mental health atlas 2020. Geneva WHO; 2020. Available: https:// www. who. int/ publi catio ns/i/item/ 97892 40036 703 [accessed 08 Feb 2022]
23 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167:268–74.
24 Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. *JAMA* 2019;321:602–3.
25 Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. *Acta Paediatr* 2007;96:644–7.
26 Harrell FE, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst* 1988;80:1198–202.
27 Perperoglou A, Sauerbrei W, Abrahamowicz M, *et al*. A review of spline function procedures in R. *BMC Med Res Methodol* 2019;19:46.
28 Rao SJ. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. *J Am Stat Assoc* 2003;98:257–8.
29 Sperry JL, Cotton BA, Luther JF, *et al*. Whole Blood Resuscitation and Association with Survival in Injured Patients with an Elevated Probability of Mortality. *J Am Coll Surg* 2023;237:206–19.
30 Feeney EV, Morgan KM, Spinella PC, *et al*. Whole blood: Total blood product ratio impacts survival in injured children. *J Trauma Acute Care Surg* 2024;97:546–51.
31 Hosseinpour H, Stewart C, Hejazi O, *et al*. FINDING THE SWEET SPOT: THE ASSOCIATION BETWEEN WHOLE BLOOD TO RED BLOOD CELLS RATIO AND OUTCOMES OF HEMORRHAGING CIVILIAN TRAUMA PATIENTS. *Shock* 2024;62:344–50.
32 Gurney JM, Staudt AM, Del Junco DJ, *et al*. Whole blood at the tip of the spear: A retrospective cohort analysis of warm fresh whole blood resuscitation versus component therapy in severely injured combat casualties. *Surgery* 2022;171:518–25.
33 Makley AT, Goodman MD, Friend LAW, *et al*. Resuscitation with fresh whole blood ameliorates the inflammatory response after hemorrhagic shock. *J Trauma* 2010;68:305–11.
34 Trivedi A, Potter DR, Miyazawa BY, *et al*. Freeze-dried platelets promote clot formation, attenuate endothelial cell permeability, and decrease pulmonary vascular leak in a murine model of hemorrhagic shock. *J Trauma Acute Care Surg* 2021;90:203–14.
35 Baucom MR, Wallen TE, Ammann AM, *et al*. Blood component resuscitative strategies to mitigate endotheliopathy in a murine hemorrhagic shock model. *J Trauma Acute Care Surg* 2023;95:21–9.
36 Shea SM, Mihalko EP, Lu L, *et al*. Doing more with less: low-titer group O whole blood resulted in less total transfusions and an independent association with survival in adults with severe traumatic hemorrhage. *J Thromb Haemost* 2024;22:140–51.
37 Malkin M, Nevo A, Brundage SI, *et al*. Effectiveness and safety of whole blood compared to balanced blood components in resuscitation of hemorrhaging trauma patients - A systematic review. *Injury* 2021;52:182–8.
38 Hanna K, Bible L, Chehab M, *et al*. Nationwide analysis of whole blood hemostatic resuscitation in civilian trauma. *J Trauma Acute Care Surg* 2020;89:329–35.