

## ORIGINAL ARTICLE

# 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

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## Abstract

**Background:** Low-titer group O whole blood (LTOWB) or component therapy (CT) may be used to resuscitate hemorrhaging trauma patients. LTOWB may have clinical and logistical benefits and may improve survival.

**Objectives:** We hypothesized LTOWB would improve 24-hour survival in hemorrhaging patients and would be safe and equally efficacious in non-group O compared with group O patients.

**Methods:** Adult trauma patients with massive transfusion protocol activations were enrolled in this observational study. The primary outcome was 24-hour mortality. Secondary outcomes included 72-hour total blood product use. A Cox regression determined the independent associations with 24-hour mortality.

**Results:** In total, 348 patients were included (CT,  $n = 180$ ; LTOWB,  $n = 168$ ). Demographics were similar between cohorts. Unadjusted 24-hour mortality was reduced in LTOWB vs CT: 8% vs 19% ( $P = .003$ ), but 6-hour and 28-day mortality were similar. In an adjusted analysis with multivariable Cox regression, LTOWB was independently associated with reduced 24-hour mortality (hazard ratio, 0.21; 95% CI, 0.07-0.67;  $P = .004$ ). LTOWB patients received significantly less 72-hour total blood products (80.9 [41.6-139.3] mL/kg vs 48.9 [25.9-106.9] mL/kg;  $P < .001$ ). In stratified 24-hour survival analyses, LTOWB was associated with improved survival for patients in shock or with coagulopathy. LTOWB use in non-group O patients was not associated with increased mortality, organ injury, or adverse events.

**Conclusion:** In this hypothesis-generating study, LTOWB use was independently associated with improved 24-hour survival, predominantly in patients with shock or coagulopathy. LTOWB also resulted in a 40% reduction in blood product use which equates to a median 2.4 L reduction in transfused products.

## KEYWORDS

blood transfusion, hemorrhage, mortality, resuscitation, trauma

## 1 | INTRODUCTION

Unintentional injury is the fourth leading cause of death in Americans of all ages, and remains the leading cause of death for individuals aged 1 to 44 years [1]. Furthermore, death from hemorrhage secondary to trauma persists as the most common cause of preventable mortality [2]. Low-titer group O whole blood (LTOWB) continues to increase in use, both in civilian and military settings, emerging as a safe and efficacious product with logistical benefits [3–6]. There are currently at least 123 verified trauma centers using LTOWB [7] and 10 pediatric hospitals [8] using or planning to use LTOWB in the United States.

LTOWB provides a more concentrated product than component therapy (CT) in a 1:1:1 unit ratio due to the reduced volume of anti-coagulants and additive solutions in whole blood compared to the amount in each constituent product of an equivalent CT transfusion [9,10]. LTOWB has increased oxygen carrying capacity (higher hemoglobin concentration), is more hemostatic (higher coagulation factors and platelet concentration), and is less acidotic relative to one unit each of red blood cells (RBCs), plasma, and whole blood-derived platelets with CT [11,12]. In addition, LTOWB contains platelets that have been stored cold (4°C). Cold-stored platelets are more hemostatically active compared with room-temperature stored platelets *in vitro*, and are currently used in CT [13,14] for actively bleeding patients in a small number of centers via a variance granted by the US Food and Drug Administration. Bacterial contamination risk is therefore partially mitigated with the use of LTOWB, and donor exposure is also reduced [15]. In addition, the use of only one bag of LTOWB over the multiple bags and vascular access needed with CT simplifies the logistics of transfusion, potentially resulting in more rapid administration of therapy in the field and at the bedside; therefore, LTOWB may ultimately improve outcomes in a situation where every minute counts [15,16]. This logistic benefit of LTOWB is theoretically amplified in the prehospital phase of resuscitation, where deaths from hemorrhage are most common and providing all blood components is not feasible [2].

We previously published the initial report of this study using data from 86 patients [17]. We now have collected and analyzed data from 348 patients, inclusive of the original cohort. The primary objective of this hypothesis-generating study was to compare 24-hour mortality between patients transfused with LTOWB or CT, and secondary objectives included comparing organ injury and total amount of all blood products transfused within the first 72 hours from admission. A unique addition in this report is the comparison in differences of measures of safety between group O vs non-group O recipients of LTOWB. We hypothesized that the use of LTOWB would be independently associated with improved 24-hour survival compared with the exclusive use of CT in adult patients with traumatic hemorrhagic shock, and that this benefit would be most apparent in patients with measurable hemostatic dysfunction at time of admission. We also hypothesized that the use of LTOWB in non-group O patients would be safe and not associated with increased adverse outcomes.

### Essentials

- Low-titer group O whole blood (LTOWB) is increasing in use, yet questions about safety and efficacy remain.
- Massively bleeding trauma patients received either component therapy or LTOWB in this observational study.
- LTOWB was associated with improved survival which was most evident in patients with coagulopathy or shock.
- Use of LTOWB in non-type O patients was safe as measured by survival, adverse events, and organ dysfunction.

## 2 | METHODS

### 2.1 | Study design

This single-center prospective observational study with a historical control was designed in July 2018 with a combination of retrospective and prospective data collection in the CT group. Data were collected from charts of patients with massive transfusion protocol (MTP) activations under a waiver of informed consent (IRB #201909200). Patients were enrolled if they were 18 years of age or older and their MTP activation was secondary to traumatic injury. On December 12, 2018, the Barnes-Jewish Hospital (BJH) MTP protocol was updated to include LTOWB. Data for the CT group were collected on patients exclusively transfused CT from January 3, 2017 to December 5, 2018. Data collection was retrospective from January 2017 to August 2018 and prospective from August 2018 to December 2018. Patients in the LTOWB group were enrolled from December 12, 2018 to July 15, 2020. Patients were excluded if a blood product was not transfused, which may have been due to early death or if LTOWB was not transfused after December 12, 2018. Patients were also excluded if they expired within 1 hour of arrival due to unsalvageable injury, as has been done in recent similar studies [18]. LTOWB use in the MTP protocol was limited to 8 units, and therefore, patients who were still bleeding and needed additional transfusions in the LTOWB group could have received CT during the MTP activation.

During the study period, LTOWB was supplied to BJH by the American Red Cross; LTOWB was leukoreduced with the TerumoBCT IMUFLEX platelet-sparing filter (Terumo) and stored in CPD. The anti-A and -B titer for all LTOWB units was <200. The shelf life for LTOWB used in this study at the BJH blood bank was 21 days. All LTOWB units were Rh+.

### 2.2 | Data collection

Data were collected and managed using the Research Electronic Data Capture electronic data capture tools hosted at Washington University in St. Louis School of Medicine [19,20]. Data collected include

demographic information including information about the injury sustained, all blood products transfused through 72 hours post-admission, daily laboratory results up through 72 hours post-admission, Multiple Organ Dysfunction Score (MODS), adverse event incidence, and mortality through discharge (time to death defined to the nearest 6 minutes [0.1 hour]) [21]. Maximum MODS for the 72-hour period were also compared. Admission laboratory values had results generated within 30 minutes of patient arrival; no laboratory values at admission or during the 72 hours period were collected specifically for the study, but rather only as part of standard care. Blood product data (number of units, product blood type) were extracted from the BJH blood management system database. A small number of patients had laboratory findings with values outside of the detectable range, which are summarized in [Supplementary Table S1](#). Values above or below the detectable limit were taken as the detectable limit to facilitate inclusion in the analysis. Intensive care unit (ICU)-free days were calculated as 28 minus the number of days in the ICU (range, 0-28 days), and assigned 0 ICU-free days for death within 28 days [22]. Patients who survived to discharge were assumed alive at 28 days.

### 2.3 | Statistical analysis and model selection

Statistical analyses were performed in RStudio (version 2021.09.0; R version 4.1.1; supplemental packages: “survival,” “survminer,” “dplyr,” “readxl,” “ggplot2,” “coxphw,” “xlsx,” and “autothresholdr”) [23–29]. Categorical data are displayed as amount over total and percentage of total and compared using Fisher’s exact test. Continuous data are displayed using medians and interquartile ranges and compared using the Wilcoxon Rank Sum test, unless otherwise indicated. Missingness is indicated, if applicable, by the number of patients who had a given test result.

Survival analyses for all mortality outcomes were performed using Kaplan–Meier curves. Survival analyses were performed unadjusted for the entire cohort and also stratified by parameters of interest to examine the impact of LTOWB vs CT in specific subsets of the patient population. To adjust for survival, a Cox regression model was fit. Univariate Cox regression was performed with 24-hour mortality as outcome. To select the final adjusted model, all parameters from the univariate analysis with  $P$  value  $\leq .05$  for 24-hour mortality were selected, and Pearson’s  $R$  was calculated between all pairs of selected parameters. Multivariable Cox regression was performed with backward stepwise selection to arrive at a fitted model. Cox models enable investigation of the effects of multiple continuous and categorical covariates on survival, accounting for possible confounders, thereby offering advantages over log-rank tests when comparing survival [30]. Highly co-linear parameters were eliminated from the model selection ( $R^2 > 0.7$ ) prioritizing variables with reduced missingness. Age and injury severity score (ISS) were forced into the initial model given their clinical importance and association with mortality after injury, as well as their consideration as essential for best practice in trauma risk adjustment [31–34]. Patients with any missing covariate(s) were not included in the model. Backward stepwise selection was then

employed to arrive at the final fitted model, by eliminating the covariate with the highest  $P$  value, refitting the new model, and repeating the process until all covariates were significant ( $P$  value cutoff = .05) aside from forced-in covariates (age and ISS). Model selection is shown in [Supplementary Table S2](#). The final model included the treatment group, LTOWB use, and covariates ISS, age, admission Glasgow Coma Scale (GCS) scores, admission platelet count, and admission maximum clot firmness (MCF). LTOWB or CT use were then also used as strata with the same covariate selection for the Cox Regression model to generate a model for survival curve visualization out to 28 days.

## 3 | RESULTS

A total of 384 trauma patients had MTP activations during the study period. Thirty-six patients were excluded due to unsalvageable injuries (expired within 1 hour of hospital arrival). Of the remaining 348 patients included in this study, 180 received hemostatic resuscitation with CT post-MTP activation, and 168 received hemostatic resuscitation with LTOWB post-MTP activation.

[Table 1](#) summarizes the epidemiologic information of each cohort. Penetrating injury occurred in 108/180 (60%) and 118/168 (70%) of the CT and LTOWB cohorts, respectively ( $P = .089$ ). Most patients were male (CT, 142/180 (79%); LTOWB 129/168 (77%);  $P = .699$ ), and the median age was 29 years (IQR, 23-41) in the CT cohort and 32 (24-44;  $P = .089$ ) in the LTOWB cohort. There was also a high frequency (69%-74%) of African Americans in both study groups. The ISS was 22 (17-34) and 22 (13-33) in the CT and LTOWB cohorts, respectively ( $P = .185$ ). Systolic blood pressure and GCS scores at admission were not statistically different ( $P = .241$  and  $P = .586$ , respectively), and the majority of baseline laboratory findings were also similar. A small number of baseline parameters were statistically significantly different (abbreviated injury scale [AIS] – lower extremities [ $P = .021$ ], partial thromboplastin time [PTT] [ $P = .023$ ], platelet count [ $P = .016$ ], and rotational thromboelastometry [ROTEM] MCF [ $P = .008$ ]). However, we do not anticipate bias in clinical results with respect to these differences due to the small absolute differences in the medians of these parameters, for example, differences of 26.9 and 25.5 for PTT in the CT and LTOWB groups, respectively.

[Table 2](#) summarizes treatments. As expected, the LTOWB group received statistically significantly lower weight-adjusted total volumes of RBCs, platelets, plasma, and cryoprecipitate over 72 hours (units and volumes are reported in [Supplementary Table S3](#)). Increased 72-hour saline and albumin volumes were given to patients in the CT cohort. TXA was administered as a 1 g i.v. bolus to 56 of 180 (31%) CT patients and 41 of 168 (24%) LTOWB patients ( $P = .189$ ).

Secondary outcomes are listed in [Table 3](#). The LTOWB group received approximately a median of 30 mL/kg less total blood products than the CT group ( $P < .001$ ) within the first 72 hours after admission ([Table 3](#)). Furthermore, 312 (172 CT, 140 LTOWB) patients were included in the transfused weight-normalized volume comparison. ICU-free days and max MODS score were not statistically

TABLE 1 Epidemiology and baseline patient characteristics.

Parameter	Sample size	CT cohort (N = 180)	Sample size	LTOWB cohort (N = 168)	Significance
<i>Patient descriptors</i>	<i>n</i>	<i>n (%) or median (IQR)</i>	<i>n</i>	<i>n (%) or median (IQR)</i>	<i>P</i>
Sex					.699
Male		142/180 (79%)		129/168 (77%)	
Female		38/180 (21%)		39/168 (23%)	
Injury					.089
Blunt		67/180 (37%)		48/168 (29%)	
Penetrating		108/180 (60%)		118/168 (70%)	
Blunt and penetrating		3/180 (2%)		1/168 (1%)	
Blunt and burn		2/180 (1%)		0/168 (0%)	
Blunt, penetrating, and burn		0/180 (0%)		0/168 (0%)	
Race					.084
Black or African American		124/180 (69%)		125/168 (74%)	
White or Caucasian		54/180 (30%)		35/168 (21%)	
Asian		0/180 (0%)		1/168 (1%)	
Other or Unknown		2/180 (1%)		7/168 (4%)	
ISS	175	22 (17-34)	160	22 (14-34)	.185
AIS	175		160		
Head		0 (0-2)		0 (0-0)	.324
Face		0 (0-1)		0 (0-0)	.529
Neck		0 (0-0)		0 (0-0)	.207
Thorax		2 (0-3)		3 (0-3)	.533
Abdomen		2 (0-4)		2 (0-3)	.368
Spine		0 (0-2)		0 (0-2)	.308
Upper extremities		0 (0-2)		0 (0-1)	.828
Lower extremities		1 (0-3)		0 (0-3)	.021
External		0 (0-0)		0 (0-0)	.623
Other trauma		0 (0-0)		0 (0-0)	NA
<b>Admission Variables</b>	<b>n</b>	<b>median (IQR)</b>	<b>n</b>	<b>median (IQR)</b>	<b>P</b>
Age, y	178	29 (23-41)	168	32 (24-44)	.089
Weight, kg	172	80 (70-95)	140	80 (71-92)	.953
BMI	169	26 (23-31)	134	26 (23-30)	.647
<b>Baseline laboratory results</b>	<b>n</b>	<b>median (IQR)</b>	<b>n</b>	<b>median (IQR)</b>	<b>P</b>
SBP, mmHg	152	84 (68-102)	128	86 (74-110)	.241
GCS	148	13 (3-15)	157	14 (3-15)	.586
Creatinine, mg/dL	134	1.21 (1.03-1.41)	136	1.28 (1.11-1.46)	.063
BUN, mg/dL	133	12 (9-16)	135	12 (10-15)	.991
PTT, sec	138	26.9 (23.3-36.2)	123	25.5 (23.7-29.0)	.023
PT, sec	138	13.4 (12.0-14.8)	122	12.7 (11.9-14.0)	.051
INR	138	1.21 (1.09-1.35)	122	1.19 (1.10-1.30)	.620

(Continues)

TABLE 1 (Continued)

Baseline laboratory results	n	median (IQR)	n	median (IQR)	P
Hb, g/dL	154	11.6 (10.1-12.9)	128	11.9 (10.6-12.9)	.183
Platelet count, X10 <sup>3</sup> cells/ $\mu$ L	154	202 (160-294)	128	234 (192-285)	<b>.016</b>
Base excess, mEq/L	45	-7 (-14-5)	113	-6 (-12-4)	.240
Lactate, mmol/L	120	5.9 (3.9-9.1)	94	5.7 (3.6-9.1)	.469
ROTEM CT, sec	136	71 (62-86)	118	69 (60-79)	.257
ROTEM $\alpha$ , °	129	69 (63-73)	116	71 (65-74)	.109
ROTEM MCF, mm	135	57 (50-63)	118	60 (54-66)	<b>.008</b>
ROTEM LI30	134	100 (99-100)	118	100 (100-100)	.281

Any *P* value that reached significance is shown in bold italic. The reported parameters are split into their respective cohort. Parameters are reported either as *n* (%) or as median IQR, where indicated. The additional column to the left of parameter values gives the *n* of patients with a value for a given parameter. Only patients with reported values were included in median (IQR) calculations. AIS, Abbreviated Injury Scale; BMI, body mass index; BUN, blood urea nitrogen; CT, component therapy; CT, clotting time; GCS, Glasgow Coma Score; Hb, hemoglobin; INR, international normalized ratio; ISS, Injury Severity Score; LI30, lysis index at 30 minutes; LTOWB, low-titer group O whole blood; MCF, maximum clot firmness; PT, prothrombin time; PTT, partial thromboplastin time; SBP, systolic blood pressure.

significantly different between groups (Table 3). The LTOWB cohort had increased survival at 24 hours (13/168 [8%] deaths vs 34/180 [19%] deaths in the CT group, *P* = .003) but not at 6 hours nor at 28 days.

Univariate regression results are shown in Supplementary Table S4. Univariate regression for the primary outcome of 24-hour mortality was significant for ISS, AIS-head, AIS-face, AIS-abdomen, age, GCS, creatinine, BUN, PTT, PT, international normalized ratio (INR), platelet count, base deficit, ROTEM CT, ROTEM  $\alpha$ , ROTEM MCF, and ROTEM LY30. These parameters were considered for the multivariate Cox regression model. The final selected model (Table 4) found use of LTOWB was associated with decreased hazard of mortality (hazard ratio [HR], 0.21; *P* = .004) when adjusted for ISS, age, admission GCS, admission platelet count, and admission MCF. Of the total 348 patients, 193 (97 CT, 96 LTOWB) had a complete set of covariate data, and thus were included in the model. Interaction terms were checked and were not significant, and therefore were excluded from the final model. The model passes the proportional hazards check (treatment group *P* = .20, global *P* = .36). The adjusted survival curves for LTOWB vs CT are shown in Figure 1. The epidemiologic data and covariate distribution for the 193 patients included in the model is shown in Supplementary Table S5.

Previously, we identified through stratified unadjusted analysis that MCF served as an indicator of the effectiveness of LTOWB, which had a greater association with survival vs CT in the coagulopathic population [17]. We therefore wanted to further investigate the effects of important clinical parameters on the effects of LTOWB on survival via stratification to better understand which patient populations might benefit most from this treatment. Patient cohorts were stratified by base excess, lactate, GCS, ISS, PTT, INR, MCF, platelet count, biological sex, and age (Figure 2 and Supplementary Figure S2). Admission base excess, GCS, PTT, MCF, INR, and platelet count all have distinct significant effects on survival at 24 hours and 28 days in

the entire patient population, while lactate, ISS, biological sex, and age did not (Figure 2 and Supplementary Figure S2). When further stratified, LTOWB vs CT treatment did not have an association with survival in patients with GCS  $\leq$  13 vs patients with GCS  $>$  13, on patients with ISS  $\leq$  20 vs ISS  $>$  20, with platelet count  $>$  150 vs platelet count  $\leq$  150, nor on male vs female patients. LTOWB vs CT treatment did have a treatment-specific association, with LTOWB independently associated with improved survival over CT in the patients with shock or coagulopathy; stratified by base excess  $\leq$  -7.5 vs base excess  $>$  -7.5, patients with PTT  $>$  26 vs PTT  $\leq$  26 and INR  $>$  1.2 vs INR  $\leq$  1.2, patients with MCF  $\leq$  60 vs MCF  $>$  60.

To determine if there was any difference in outcomes between group O and non-group O recipients of LTOWB, we examined differences in outcomes between these 2 subgroups. Epidemiologic information, laboratory findings, blood products transfused, and outcomes are summarized in Table 5. There were statistical differences in injury type and age between study groups with increased age and less penetrating injury in the non-group O patients. There were no differences between patient sex, ISS, weight, and BMI between study groups. All baseline laboratory values were not significantly different except for ROTEM  $\alpha$ , which was 58 (52-62) in the group O and 61 (58-67) in the non-group O (*P* = .021). Maximum creatinine values within 72 hours were not different between subgroups. LTOWB transfused and total blood products transfused over 72 hours were also not different, and no outcomes, including any MODS sub-scores, were statistically different between group O and non-group O recipients of LTOWB.

## 4 | DISCUSSION

We report in an adjusted analysis that use of LTOWB over CT in hemostatic resuscitation of massively bleeding patients resulted in an

TABLE 2 Treatments.

Parameter	Sample size	CT cohort (N = 180)	Sample size	LTOWB cohort (N = 168)	Significance
<i>Blood Product Volumes (72 hours), weight-adjusted</i>	<i>n</i>	<i>median (IQR)</i>	<i>n</i>	<i>median (IQR)</i>	<i>P</i>
LTOWB, mL/kg			140	31 (13-45)	
RBCs, mL/kg	172	51 (27-83)	140	12 (5-33)	<b>&lt;.001</b>
Platelets, mL/kg	172	4 (0-11)	140	0 (0-6)	<b>&lt;.001</b>
Plasma, mL/kg	172	26 (12-45)	140	4 (0-18)	<b>&lt;.001</b>
Cryoprecipitate, mL/kg	172	0 (0-3)	140	0 (0-0)	<b>.040</b>
<i>Other treatments</i>	<i>n</i>	<i>n (%) or median (IQR)</i>	<i>n</i>	<i>n (%) or median (IQR)</i>	<i>P</i>
Normal saline, n received		157/180 (87%)		149/168 (87%)	.743
Volume, mL	180	2651 (1000-5272)	168	2000 (604-4094)	<b>.032</b>
Weight-adjusted volume, mL/kg	172	32 (12-70)	140	23 (8-50)	<b>.014</b>
Lactated Ringer's, n received		147/180 (82%)		143/168 (85%)	.472
Volume, mL	180	3113 (1000-6204)	168	3460 (1000-6383)	.674
Weight-adjusted volume, mL/kg	172	42 (11-80)	140	37 (12-75)	.881
Total crystalloid fluids, n received		164/180 (91%)		157/168 (93%)	.431
Volume, mL	180	6964 (3912-11049)	168	6771 (3523-9716)	.512
Weight-adjusted volume, mL/kg	172	88 (48-144)	140	79 (42-121)	.201
Albumin, n received		96/180 (53%)		75/168 (45%)	.109
Volume, mL	180	250 (0-1000)	168	0 (0-750)	.093
Weight-adjusted volume, mL/kg	172	3 (0-11)	140	0 (0-9)	<b>.047</b>
TXA, n received		56/180 (31%)		41/168 (24%)	.189
TXA bolus dose, g	51	1 (1-1)	36	1 (1-1)	.512
TXA infusion use, n		13/192 (7%)		12/192 (6%)	.201
TXA infusion dose, g	11	1 (1-1)	8	1 (1-1)	.416
Calcium, n received		164/180 (91%)		148/168 (88%)	.383
Total, g	180	4 (2-8)	168	4 (2-8)	.870
Weight-adjusted 72-hour total dose, mg/kg	172	49 (22-97)	140	44 (17-98)	.370

Any *P* value that reached significance is shown in bold italic. Blood products transfused separated by specific component or LTOWB over 72 hours are reported as weight-adjusted totals (median [IQR]). Saline, lactated Ringer's, total crystalloids, and albumin are shown for each cohort first as the number of patients who received the treatment and then as the median (IQR) total over 72 hours, both outright and weight-adjusted. The number of patients who received TXA and the median infusion is reported, as well as the number of those patients who also received an infusion dose and the median infusion dose. Calcium is reported first as the number of patients who received calcium, and then as both the total over 72-hours and the weight-adjusted 72-hour total. The median (IQR) values include all patients, ie, patients who did not receive the treatment were reported as 0, with the only exception being TXA doses. CT, component therapy; LTOWB, low-titer group O whole blood; RBCs, red blood cells; TXA, tranexamic acid.

independent association in reduction of risk of 24-hour mortality ( $P = .004$ ) using a Cox regression analysis in our single-center prospective observational study with a historical control. The safety of LTOWB in this population is supported by our results suggesting no differences in transfusion reactions nor stroke, and no difference in organ injury over the same period with the use of LTOWB. This safety signal was also present in non-group O recipients of LTOWB.

Use of LTOWB in hemostatic resuscitation in this patient population also resulted in a 40% reduction in total weight-normalized blood product use over the 72-hour postadmission timeframe. In other terms, the LTOWB group received approximately 30mL/kg less

of total blood products. Considering the median weight of patients in this study which was 80 kg, a 30 mL/kg reduction equates to a 2.4-L reduction in blood products transfused. This is a substantial reduction in blood use and exposure. Using a typical volume of 300 mL per unit for RBCs and apheresis unit of platelets, and 250 mL for a plasma unit, this equates to about 4 units of RBCs, 4 units of plasma, and 1 apheresis unit of platelets. Additionally, the CT cohort received approximately double the anticoagulant and additive solution volume compared with the LTOWB cohort [10], which could have deleterious consequences for patients in shock experiencing hypocoagulability. The LTOWB cohort also was exposed to on average up to roughly 8

TABLE 3 Outcomes.

Parameter	Sample size	CT Cohort (N = 180)	Sample size	LTOWB Cohort (N = 168)	Significance
	n	n (%) or median (IQR)	n	n (%) or median (IQR)	P
6-hour mortality		20/180 (11%)		12/168 (7%)	.265
24-hour mortality		34/180 (19%)		13/168 (8%)	<b>.003</b>
28-day mortality		49/180 (27%)		33/168 (20%)	.102
Total blood products, mL/kg	172	82 (44-139)	140	48 (26-108)	<b>&lt;.001</b>
ICU-free days	124	21 (0-25)	150	19 (2-25)	.639
MODS					
Respiratory	148	1 (0-3)	151	1 (0-3)	.953
Renal	148	1 (0-1)	153	1 (0-1)	.496
Hepatic	148	0 (0-1)	151	0 (0-1)	.905
Cardiologic	148	0 (0-0)	151	0 (0-0)	<b>.034</b>
Hematologic	148	1 (1-2)	151	1 (0-2)	<b>.036</b>
Neurologic	148	3 (1-4)	151	4 (3-4)	<b>.004</b>
Total Score	148	6 (4-8)	152	7 (4-9)	.223
Transfusion reaction		4 (2%)		3 (2%)	1.000
Stroke within 72 hours		3 (2%)		7 (4%)	.208

Outcomes are reported as n (%) or median (IQR) where indicated. Significant P values are shown in bold italic. CT, component therapy; ICU, intensive care unit; LTOWB, low-titer group O whole blood; MODS, Multiple Organ Dysfunction Score.

fewer unique donors, potentially reducing infectious and noninfectious risks of transfusion.

Blood management has become a very important principle, due in part to the improved patient outcomes associated with reducing blood product exposure for patients who may not benefit from transfusion. It is now also essential due to the national blood shortage crisis where there is not enough supply of group O RBCs and platelets due to both the aging donor pool, thereby reducing blood donor availability, and the increased use of blood products for bleeding patients [35,36]. The risks resulting from a national blood shortage and consequences for patients with traumatic injury have been recently described [35]. Our results demonstrating the use of LTOWB seems to “do more with less”

TABLE 4 Multivariate Cox Regression results.

Cox Regression	24-hour adjusted mortality		
	HR	95% CI	P
Survival predictor			
LTOWB use	0.21	(0.07, 0.61)	<b>.004</b>
ISS	0.98	(0.95, 1.01)	.124
Age	1.02	(0.99, 1.04)	.199
GCS	0.92	(0.86, 1.00)	<b>.043</b>
Plt Count	0.99	(0.99, 1.00)	<b>.049</b>
MCF	0.96	(0.94, 0.99)	<b>.004</b>

The selected model was applied to 24-hour mortality and the resulting HR, 95% CI, and P values are shown. N = 193 (96 component therapy, 97 LTOWB). If P values achieved significance they are shown in bold italic. GCS, Glasgow Coma Scale; HR, hazard ratio; MCF, maximum clot firmness; LTOWB, low-titer group O whole blood; Plt, platelet.

is critical for this patient population with a high rate of preventable death from hemorrhage and increased risk of nonavailability of blood products for resuscitation of life-threatening hemorrhage [35,37].

Our findings of independent association with LTOWB and improved survival while also using fewer total blood products are consistent with other reports of cold-stored LTOWB in adult and

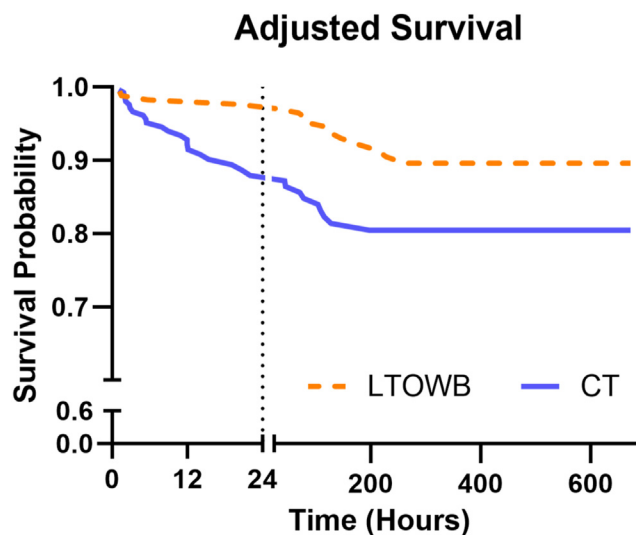
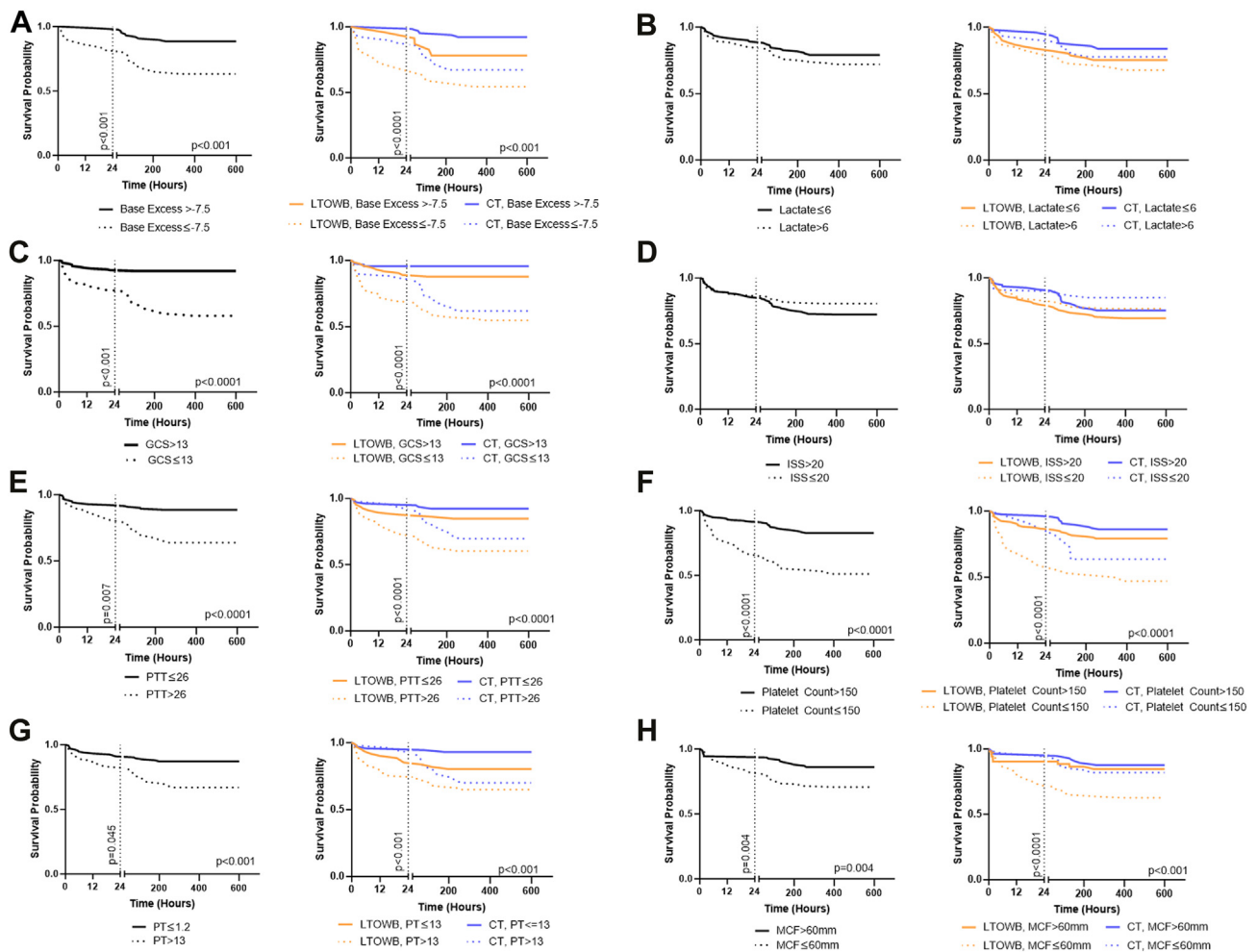


FIGURE 1 Low-titer group O whole blood (LTOWB) use is associated with improved survival in an adjusted model. The association is significant at 24 hours (Cox regression  $P = .004$ ). Survival adjusted by injury severity score, age, Glasgow Coma Score (GCS), admission platelet count, and admission maximum clot firmness (bottom). N = 193 (96 component therapy [CT], 97 LTOWB).



**FIGURE 2** Further stratified survival demonstrates which patient populations may most benefit from use of low-titer group O whole blood (LTOWB) over component therapy (CT). Black curves at left stratify survival out to 28 days (672 hours) by (A) base excess, (B) lactate, (C) Glasgow Coma Scale (GCS), (D) Injury Severity Score (ISS), (E) partial thromboplastin time (PTT), (F) platelet count, (G) prothrombin time (PT), and (H) maximum clot firmness (MCF), while the colored curves at right further stratify within those groups by those who received LTOWB vs CT. The vertical dashed line is at 24 hours. If survival was significantly different at 24 hours, the *P* value (log-rank test) is along the dashed line. If survival was significantly different at 28 days, the *P* value is shown in the bottom right of the curve. Only significant *P* values are shown. INR, international normalized ratio.

pediatric trauma patients [6,8,10,38,39]. Recently, Brill et al. [6] reported a 4-fold survival benefit and 60% reduction in overall transfusions with use of LTOWB over CT in emergency release blood products in a large (nearly 1380 patients) single-center prospective observational cohort design. There are a few interesting differences among our studies. Of note, the LTOWB used at our institution was leukoreduced (LR) with a platelet-sparing filter, while the LTOWB used in the study by Brill et al. [6] was not. We have previously reported on some minor measurable differences in some *in vitro* measures of hemostasis in older LR WB (days 14-21) compared with non-LR WB [15]. These differences may or may not be clinically meaningful. As we observed a substantial independent association with improved survival, and 2 of our final selected covariates (platelet count and MCF) directly implicate the critical role of the platelet in this patient population, this supports the use of a platelet-sparing LR filter. Randomized controlled trials must be done to fully understand

the impact of blood product manufacturing methods, to include LR of LTOWB, on *in vivo* function and clinical outcomes. Use of LTOWB has also been shown to be of benefit in pediatric patients. Use of LTOWB over individual blood components in children with severe traumatic bleeding more rapidly provides RBCs, plasma, and platelets; more effectively resolves shock and coagulopathy; is associated with less total amount of blood products administered [39] and mechanical ventilation days; and is independently associated with reduced 72-hour (OR, 0.23; [0.08-0.70]), and 28-day mortality (OR, 0.41; [0.23 to 0.98]) in a single-center retrospective study [8].

The additional stratification in survival analyses indicated there may be patient populations that might benefit most from LTOWB over CT transfusion. We had previously identified MCF as a striking predictor of mortality in preliminary analysis of a small initial subset (approximately 40 patients per group) of these cohorts, and even more interestingly, LTOWB had a distinct substantial benefit



TABLE 5 Group O and non-group O recipients of LTOWB.

Parameter	Sample size	Group O (N = 64)	Sample size	Non-group O (N = 87)	Significance
<i>Patient descriptors</i>	<i>n</i>	<i>n (%) or median (IQR)</i>	<i>n</i>	<i>n (%) or median (IQR)</i>	<i>P</i>
Sex					.846
Male		52/64 (81%)		68/87 (78%)	
Female		12/64 (19%)		19/87 (22%)	
Injury					.009
Blunt only		10/64 (18%)		33/87 (37%)	
Penetrating only		52/64 (79%)		54/87 (63%)	
Blunt and penetrating		1/64 (1%)		0/87 (0%)	
Blunt, penetrating, and burn		0/64 (0%)		0/87 (0%)	
ISS	59	25 (16-34)	84	22 (13-34)	.131
<b>Admission variables</b>	<b><i>n</i></b>	<b><i>median (IQR)</i></b>	<b><i>n</i></b>	<b><i>median (IQR)</i></b>	<b><i>P</i></b>
Age, y	64	30 (23-41)	87	33 (25-48)	.036
Weight, kg	55	80 (73-90)	76	80 (70-94)	.465
BMI	53	26 (22-30)	73	25 (23-29)	.865
<b>Baseline laboratory findings</b>	<b><i>n</i></b>	<b><i>median (IQR)</i></b>	<b><i>n</i></b>	<b><i>median (IQR)</i></b>	<b><i>P</i></b>
SBP, mmHg	46	84 (69-105)	72	86 (76-108)	.373
GCS	62	14 (7-15)	80	14 (3-15)	.868
Creatinine, mg/dL	53	1.30 (1.16-1.57)	76	1.28 (1.14-1.41)	.215
BUN, mg/dL	53	12 (9-14)	75	12 (10-15)	.425
PTT, sec	47	25.7 (24.2-29.3)	69	25.5 (23.0-28.0)	.260
PT, sec	46	12.9 (11.9-14.2)	69	12.6 (12.0-13.8)	.668
INR	46	1.20 (1.10-1.30)	69	1.18 (1.10-1.30)	.621
Hb, g/dL	50	11.8 (10.1-12.8)	71	12.1 (11.3-13.1)	.094
Platelet count, $\times 10^3$ cells/ $\mu$ L	50	235 (195-266)	71	233 (185-289)	.875
Base excess, mEq/L	44	-6 (-14-4)	62	-7 (-12-4)	.890
Lactate, mmol/L	36	6.0 (3.2-9.0)	50	5.2 (3.6-8.9)	.937
ROTEM CT, sec	48	72 (59-82)	64	68 (62-78)	.467
ROTEM MCF, mm	47	69 (64-74)	63	71 (68-74)	.114
ROTEM $\alpha$ , °	48	58 (52-62)	64	61 (58-67)	.021
ROTEM LI30	48	100 (99-100)	64	100 (100-100)	.250
<b>Laboratory findings</b>		<b><i>median (IQR)</i></b>		<b><i>median (IQR)</i></b>	<b><i>P</i></b>
Creatinine day 1, mg/dL	58	1.26 (0.99-1.99)	81	1.25 (0.97-1.72)	.531
Creatinine day 2, mg/dL	53	1.15 (0.93-2.14)	73	1.07 (0.94-1.52)	.242
Creatinine day 3, mg/dL	53	1.03 (0.86-1.75)	68	0.97 (0.82-1.25)	.138
Maximum creatinine over 3 days, mg/dL	64	1.21 (0.98-1.84)	87	1.23 (0.98-1.68)	.756
<b>Treatments (Over 3 days)</b>		<b><i>median (IQR)</i></b>		<b><i>median (IQR)</i></b>	<b><i>P</i></b>
LTOWB transfused (mL/kg)	55	31 (14-44)	76	27 (13-46)	.830
LTOWB+RBC (mL/kg)	55	44 (30-97)	76	39 (23-67)	.205
Total blood products transfused (mL/kg)	55	49 (31-139)	76	46 (25-82)	.221

Outcomes	<i>n</i> (%) or median (IQR)		<i>n</i> (%) or median (IQR)		<i>P</i>
6-hour mortality	3/64 (5%)		2/87 (2%)		.423
24-hour mortality	3/64 (5%)		3/87 (3%)		.712
28-day mortality	9/64 (14%)		16/87 (18%)		.483
Max MODS over 3 days					
Respiratory	59	1 (0-3)	83	1 (0-3)	.769
Renal	61	1 (0-1)	83	1 (0-1)	.375
Hepatic	59	0 (0-1)	83	0 (0-1)	.498
Cardiologic	59	0 (0-0)	83	0 (0-0)	.315
Hematologic	59	1 (0-2)	83	1 (0-2)	.444
Neurologic	59	4 (3-4)	83	4 (3-4)	.754
Total Score	60	6 (4-9)	83	7 (5-9)	.982

Epidemiology, baseline laboratory values, maximum daily creatinine values and maximum creatinine value over 72 hours, treatments, and outcomes are shown for recipients of LTOWB separated into group O and non-group O subcohorts. *P* values that reached significance are shown in bold italic. BMI, body mass index; BUN, blood urea nitrogen; CT, clotting time; GCS, Glasgow Coma Score; Hb, hemoglobin; INR, international normalized ratio; ISS, injury severity score; LI30, lysis index at 30 minutes; LTOWB, low-titer group O whole blood; MCF, maximum clot firmness; MODS: Multiple Organ Dysfunction Score; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cells; SBP, systolic blood pressure.

specifically in coagulopathic patients (MCF < 60) [17]. Interestingly, we see that trend conserved, both with MCF as well as with PTT, where LTOWB use over CT was independently associated with improved survival at 24 hours in patients with low MCF (<60 mm) and high PTT (>26 s). This supports the use of LTOWB for hemostatic resuscitation in this patient population and potentially, especially in the trauma-induced coagulopathy population. This also may indicate a precision medicine application, and that in the case of product shortages, hypocoagulable patients could be prioritized to receive LTOWB. However, it is important to note that access to assays and turnaround time may be a major limiting factor in implementation of such an approach. Prehospital laboratory results, if available, would be most informative for hemostatic resuscitation, however, we recognize this is not available at many institutions. Better point-of-care devices that are rapid, easy to use, and could be deployed prehospital would help identify patients most in need of transfusion early in their course of care. At minimum, perhaps lab results could help current practitioners tailor an MTP activation, or initiate an MTP if one has not been started already once results are received.

While there is a small association with improved survival at 24 hours due to LTOWB in patients with low platelet counts, it is less in magnitude than seen in the functional hemostatic assays. This is consistent with the hypothesis that one of the mechanisms by which LTOWB increases survival is in rescue of hemostatic mechanism, as a low platelet count alone does not necessarily indicate that platelets are nonfunctional. Acidotic patients (base excess < -7.5, ie, those in shock) also had a significant survival benefit in use of LTOWB over CT. The same trend, but to a lesser extent, was seen in patients with high lactate (>6 mg/dL). The reduced citrate load with a LTOWB resuscitation that leads to less total blood use is likely contributory to reducing the deleterious effects of acidosis [40]. ISS did not significantly predict survival at any timepoint in our patient population, as seen both in our

Cox model and in the unadjusted survival curve, and survival does not appear to be associated with treatment when further stratified by this parameter alone. This may be due to our high penetrating injury case-mix, in which ISS is known to underestimate injury severity [41]. Biological sex was also not impactful on 24-hour and 28-day survival and did not see changes when further stratified by treatment, and age alone was not significant in our analyses; however, again this may be due to case-mix with a relatively young cohort.

Conventional practice historically has dictated that females of childbearing potential (FCP) whom are RhD- should receive RhD- blood products, due to a concern that alloimmunization will result in a risk for the loss of a future RhD+ fetus. Of the 39 women who received CT, 5 were RhD-. One woman received RhD+ RBC, and that patient was an FCP. At our center, all LTOWB supplied is RhD+. Of the 42 women who received LTOWB, 4 were RhD-, 2 of which were FCP. Relative to the use of CT, the implementation of LTOWB only resulted in one additional transfusion of an RhD-incompatible product to a massively bleeding FCP. Notably, recent analysis demonstrates the actual probability of an RhD- FCP experiencing fetal demise or significant neurologic morbidity from hemolytic disease of the fetus and newborn (HDFN) due to alloimmunization in this context to be approximately 0.3% [42]. Recent reviews on this topic suggest that the increased use of Rh+ LTOWB which may both reduce the use of total blood products and improve survival justifies exposing FCP to the risk of HDFN [43]. Large surveys of women and parents of female children strongly agree with this concept [44,45].

There are some limitations to consider in our study. There may have been unmeasured confounders on outcomes that we did not include in our analysis and the lack of randomization increases the risk of bias. The time at which blood products were administered was not able to be collected prospectively, therefore we cannot confirm that all admission laboratory results were collected prior to any

transfusion. Of note, laboratory findings were recorded at admission within half an hour, which minimized this concern. We did not collect information on pharmacologic agents such as antiplatelet medications or anticoagulants. We have presented an adjusted analysis alongside others and direct reporting of unadjusted outcomes to provide a complete review of the data. Due to missingness, the final selected model supporting the benefits of LTOWB contains 193 out of the 348 total patients (55%). While these 97 CT and 96 LTOWB patients included in the model had largely similar epidemiology and had no statistically significant nor clinically significant differences in covariates, the LTOWB did have higher median values for all covariates which may be a source of bias. We also did not fit additional models for secondary outcomes, including other mortality timepoints, and as such, we chose this model as informative with the aim of saving further detailed analysis for a subsequent study or trial. While we did not find any acute safety signal, future studies to further characterize long-term effects of transfusion and different blood types throughout survivor lifetime are needed to fully understand any unknown potential impact. This is a hypothesis-generating study based on our single-center experience with implementation of LTOWB.

## 5 | CONCLUSIONS

LTOWB use in hemostatic resuscitation of trauma patients with life-threatening bleeding was independently associated with reduced 24-hour mortality at our center, while also being transfused with a median of 30 mL/kg less of 72-hour total blood products. Use of LTOWB had the greatest association with 24-hour survival in patients with shock or who were in a hypocoagulable state. The use of LTOWB in non-group O patients was not associated with an increased risk of adverse events or organ injury. These results support the use of LTOWB in this patient population. Randomized controlled trials are needed to fully examine the safety and efficacy of this LTOWB for this indication.

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## AUTHOR CONTRIBUTIONS

S.M.S. cleaned the database, analyzed data, generated tables and figures, and wrote the first draft of the manuscript. E.P.M. cleaned the database, analyzed data, generated tables and figures, and edited the manuscript. L.L. assisted with data analysis and edited the manuscript.

K.A.T. assisted with data analysis, visualization and edited the manuscript. D.S. assisted with study design, assisted with patient data collection, and edited the manuscript. J.B.B. assisted with and reviewed data analysis and statistical methodology, and edited the manuscript. G.V.B. designed the study, assisted and oversaw patient data collection, assisted with data report curation, and edited the manuscript. P.C.S. designed the study, provided funding, coordinated the effort, reviewed data analysis and visualization, and edited the manuscript.

## DECLARATION OF COMPETING INTERESTS

P.C.S. is a consultant for Hemanext, Cerus, Haima, and Co-Founder and Chief Medical Officer for Kalocyte. The authors have no other conflicts of interest to disclose.

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## REFERENCES

- [1] Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma*. 2006;60:S3–11.
- [2] Spinella PC. Zero preventable deaths after traumatic injury: an achievable goal. *J Trauma Acute Care Surg*. 2017;82:S2–8.
- [3] Yazer MH, Cap AP, Spinella PC. Raising the standards on whole blood. *J Trauma Acute Care Surg*. 2018;84:S14–7.
- [4] Spinella PC, Cap AP. Whole blood: back to the future. *Curr Opin Hematol*. 2016;23:536–42.
- [5] Guyette FX, Zenati M, Triulzi DJ, Yazer MH, Skroczyk H, Early BJ, Adams PW, Brown JB, Alarcon L, Neal MD, Forsythe RM, Zuckerbraun BS, Peitzman AB, Billiar TR, Sperry JL. Prehospital low titer group O whole blood is feasible and safe: Results of a prospective randomized pilot trial. *J Trauma Acute Care Surg*. 2022;92:839–47.
- [6] Brill JB, Tang B, Hatton G, Mueck KM, McCoy CC, Kao LS, Cotton BA. 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.
- [7] Hashmi ZG, Chehab M, Nathens AB, Joseph B, Bank EA, Jansen JO, Holcomb JB. Whole truths but half the blood: addressing the gap between the evidence and practice of pre-hospital and in-hospital blood product use for trauma resuscitation. *Transfusion*. 2021;61:5348–53.
- [8] Gaines BA, Yazer MH, Triulzi DJ, Sperry JL, Neal MD, Billiar TR, Leeper CM. Low titer group O whole blood in injured children requiring massive transfusion. *Ann Surg*. 2023;277:e919–24.
- [9] Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma*. 2009;66:S69–76.
- [10] Seheult JN, Anto V, Alarcon LH, Sperry JL, Triulzi DJ, Yazer MH. Clinical outcomes among low-titer group O whole blood recipients compared to recipients of conventional components in civilian trauma resuscitation. *Transfusion*. 2018;58:1838–45.
- [11] Armand R, Hess JR. Treating coagulopathy in trauma patients. *Transfus Med Rev*. 2003;17:223–31.
- [12] Zielinski MD, Jenkins DH, Hughes JD, Badjie KS, Stubbs JR. Back to the future: the renaissance of whole-blood transfusions for massively hemorrhaging patients. *Surgery*. 2014;155:883–6.

- [13] Nair PM, Pandya SG, Dallo SF, Reddoch KM, Montgomery RK, Pidcoke HF, Cap AP, Ramasubramanian AK. Platelets stored at 4 degrees C contribute to superior clot properties compared to current standard-of-care through fibrin-crosslinking. *Br J Haematol*. 2017;178:119–29.
- [14] Reddoch KM, Pidcoke HF, Montgomery RK, Fedyk CG, Aden JK, Ramasubramanian AK, Cap AP. Hemostatic function of apheresis platelets stored at 4 degrees C and 22 degrees C. *Shock*. 2014;41:54–61.
- [15] Thomas KA, Shea SM, Yazer MH, Spinella PC. Effect of leukoreduction and pathogen reduction on the hemostatic function of whole blood. *Transfusion*. 2019;59:1539–48.
- [16] Meyer DE, Vincent LE, Fox EE, O’Keeffe T, Inaba K, Bulger E, Holcomb JB, Cotton BA. Every minute counts: time to delivery of initial massive transfusion cooler and its impact on mortality. *J Trauma Acute Care Surg*. 2017;83:19–24.
- [17] Shea SM, Staudt AM, Thomas KA, Schuerer D, Mielke JE, Folkerts D, Lowder E, Martin C, Bochicchio GV, Spinella PC. The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage. *Transfusion*. 2020;60(Suppl 3):S2–9.
- [18] 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;158:532–40.
- [19] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–81.
- [20] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
- [21] Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995;23:1638–52.
- [22] Cho H, Wendelberger B, Gausche-Hill M, Wang HE, Hansen M, Bosson N, Lewis RJ. ICU-free days as a more sensitive primary outcome for clinical trials in critically ill pediatric patients. *J Am Coll Emerg Physicians Open*. 2021;2:e12479.
- [23] R Core Team. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
- [24] Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Muller M. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12:77.
- [25] Sing T, Sander O, Beerenwinkel N, Lengauer T. ROCr: visualizing classifier performance in R. *Bioinformatics*. 2005;21:3940–1.
- [26] Wickham H, Bryan J. *Read Excel Files*. 2019.
- [27] Heinze G, Ploner M, Dunkler D. *coxphw: Weighted Estimation in Cox Regression*. R package version 4.0.2 edn, 2020.
- [28] Therneau TM, Grambsch PM. *Modeling survival data: extending the Cox Model*. New York: Springer; 2000.
- [29] Wickham H. *Ggplot2: Elegant graphics for data analysis*. R package version 3.3. 3 edn. Springer International Publishing; 2016.
- [30] Deo SV, Deo V, Sundaram V. Survival analysis-part 2: Cox proportional hazards model. *Indian J Thorac Cardiovasc Surg*. 2021;37:229–33.
- [31] Joseph B, Scalea T. The consequences of aging on the response to injury and critical illness. *Shock*. 2020;54:144–53.
- [32] Hildebrand F, Pape HC, Horst K, Andruszkow H, Kobbe P, Simon TP, Marx G, Schurholz T. Impact of age on the clinical outcomes of major trauma. *Eur J Trauma Emerg Surg*. 2016;42:317–32.
- [33] Haider AH, Hashmi ZG, Zafar SN, Castillo R, Haut ER, Schneider EB, Cornwell EE 3rd, Mackenzie EJ, Efron DT. Developing best practices to study trauma outcomes in large databases: an evidence-based approach to determine the best mortality risk adjustment model. *J Trauma Acute Care Surg*. 2014;76:1061–9.
- [34] Haider AH, Saleem T, Leow JJ, Villegas CV, Kizat M, Schneider EB, Haut ER, Stevens KA, Cornwell EE 3rd, MacKenzie EJ, Efron DT. Influence of the National Trauma Data Bank on the study of trauma outcomes: is it time to set research best practices to further enhance its impact? *J Am Coll Surg*. 2012;214:756–68.
- [35] Stein DM, Upperman JS, Livingston DH, Andrews J, Bulger EM, Cohen MJ, Eastridge BJ, Fontaine MJ, Guillaumondegui O, Hess JR, Jenkins DH, Kaups KL, Nance ML, Spinella PC, Zarza BL, Zonies D, Coimbra R. National blood shortage: a call to action from the trauma community. *J Trauma Acute Care Surg*. 2022;93:e119–22.
- [36] Stubbs JR, Homer MJ, Silverman T, Cap AP. The current state of the platelet supply in the US and proposed options to decrease the risk of critical shortages. *Transfusion*. 2021;61:303–12.
- [37] Spinella PC, Cap AP. Prehospital hemostatic resuscitation to achieve zero preventable deaths after traumatic injury. *Curr Opin Hematol*. 2017;24:529–35.
- [38] Cotton BA, Podbielski J, Camp E, Welch T, del Junco D, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, Wade CE, Holcomb JB. Early Whole Blood I. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Ann Surg*. 2013;258:527–32;discussion 32–3.
- [39] Anand T, Obaid O, Nelson A, Chehab M, Dittillo M, Hammad A, Douglas M, Bible L, Joseph B. Whole blood hemostatic resuscitation in pediatric trauma: a nationwide propensity-matched analysis. *J Trauma Acute Care Surg*. 2021;91:573–8.
- [40] Li K, Xu Y. Citrate metabolism in blood transfusions and its relationship due to metabolic alkalosis and respiratory acidosis. *Int J Clin Exp Med*. 2015;8:6578–84.
- [41] Rowell SE, Barbosa RR, Diggs BS, Schreiber MA, Trauma Outcomes G, Holcomb JB, Wade CE, Brasel KJ, Vercruyse G, MacLeod J, Dutton RP, Hess JR, Duchesne JC, McSwain NE, Muskat P, Johannigam J, Cryer HM, Tillou A, Cohen MJ, Pittet JF, et al. Specific abbreviated injury scale values are responsible for the underestimation of mortality in penetrating trauma patients by the injury severity score. *J Trauma*. 2011;71:S384–8.
- [42] Yazer MH, Delaney M, Doughty H, Dunbar NM, Al-Riyami AZ, Triulzi DJ, Watchko JF, Wood EM, Yahalom V, Emery SP. It is time to reconsider the risks of transfusing RhD negative females of child-bearing potential with RhD positive red blood cells in bleeding emergencies. *Transfusion*. 2019;59:3794–9.
- [43] Andrews J, Josephson CD, Young P, Spinella PC, Yazer MH. Weighing the risk of hemolytic disease of the newborn versus the benefits of using of RhD-positive blood products in trauma. *Transfusion*. 2023;63:S4–9.
- [44] Yu G, Siegler J, Hayes J, Yazer MH, Spinella PC. Attitudes of American adult women toward accepting RhD-mismatched transfusions in bleeding emergencies. *Transfusion*. 2022;62:S211–7.
- [45] Morgan KM, Lobo R, Annen K, Villarreal RI, Chou S, Uter S, Leonard JC, Dyer C, Yazer M, Spinella PC, Leeper CM. Parent perceptions of emergent blood transfusion in children. *Transfusion*. 2023;63:S35–45.

#### SUPPLEMENTARY MATERIAL

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