

SYSTEMATIC REVIEW META-ANALYSIS

Trauma

Whole blood transfusion versus component therapy in trauma resuscitation: a systematic review and meta-analysis

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Abstract

Background: Patients with hemorrhagic shock from trauma often require balanced blood product transfusion with red blood cells, plasma, and platelets. Resuscitation with whole blood resuscitation is becoming a common practice. We performed a systematic review and meta-analysis of studies comparing whole blood transfusion with balanced component therapy in patients suffering from traumatic hemorrhagic shock.

Methods: We searched MEDLINE Ovid, EMBASE, and the Cochrane Library for human studies comparing whole blood with component blood therapy published from January 2007 to June 2019. We included studies from both civilian and military settings and that reported 24-hour, in-hospital, or 30-day mortality. We followed the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines, assessing study quality, publication bias, and heterogeneity. We used meta-analytic models to determine the associations (odds ratio [OR] with 95% confidence interval [CI]) between whole blood transfusion and (1) 24-hour mortality, and (2) in-hospital or 30-day mortality.

Results: A total of 1759 identified studies, 12 (reporting on $n = 8431$ patients) met inclusion criteria. There was heterogeneity in the design, setting, interventions, and outcomes of the studies. On meta-analysis, whole blood transfusion was not associated with 24-hour mortality (OR = 0.83; 95% CI = 0.56–1.24) or in-hospital/30-day mortality (OR = 0.79; 95% CI = 0.48–1.31).

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Conclusion: In this systematic review and meta-analysis, compared with conventional component transfusion, whole blood was not associated with 24-hour or in-hospital mortality. However, there were important limitations with and heterogeneity among the primary studies. Additional study is needed to determine the effectiveness of whole blood.

KEYWORDS

blood products, hemorrhage, meta-analysis, systematic review, transfusion

1 | INTRODUCTION

1.1 | Background

Hemorrhage accounts for 30%–40% of total trauma deaths.¹ Blood transfusion with balanced components (red cell concentrate, plasma, platelets, and cryoprecipitate) is the current standard of care for patients suffering from hemorrhagic shock.^{2–5} The United States military is using whole blood, both out-of-hospital and in the deployed hospital setting, as a standard of care.^{6–8} Recent civilian studies report on the increasing use of whole blood as an alternate approach to trauma resuscitation with component therapy.⁶

Fresh whole blood transfusion was first widely used during World War II.⁷ In the early 1970s, advancements in the fractionation process led to component therapy becoming usual care for patients in hemorrhagic shock. Fresh whole blood transfusion saw resurgence during the wars in Iraq and Afghanistan, due to easier transfusion logistics and perceived efficacy.⁷ Whole blood is now being reintroduced into civilian trauma surgical practice, with reports of improved outcomes. Furthermore, the Joint Trauma System clinical practice guidelines recommend the use of whole blood as the preferred therapy in the out-of-hospital treatment of hemorrhagic shock.⁸

1.2 | Importance

A number of retrospective studies have reported beneficial effects of whole blood in trauma resuscitation, and there is one, small, randomized, single-center clinical trial.⁸ However, there have been few attempts to synthesize the results of the studies. A systematic review and meta-analysis of these studies could help to highlight the overarching strengths and weaknesses of existing data and estimated associations with outcomes.

1.3 | Goals of this investigation

Through a systematic review and meta-analysis of the existing literature, we sought to determine the association of whole blood with mortality after traumatic hemorrhagic shock.

2 | METHODS AND MATERIALS

We conducted a systematic review and meta-analysis according to Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁹ Using a pre-determined protocol, we performed a systematic search of the OVID Medline, EMBASE, and Cochrane Library databases for studies published from January 2007 to June 2019. The search protocol for this systematic review was registered with the University of York Center for Reviews and Dissemination and the National Institute for Health Research PROSPERO database (registration no. CRD42019136731).

2.1 | Study design and data sources

2.2 | Selection of studies

The search strategy is summarized in Appendix 1. We structured the search around the population, interest, context (PICO) framework to address the question, “In patients experiencing hemorrhagic shock due to trauma, is whole blood transfusion (compared with component therapy) associated with reduced mortality?”¹⁰ We identified studies evaluating the association of whole blood transfusion with mortality in trauma patients. Eligible studies included randomized control trials, non-randomized control trials, and retrospective or prospective cohort studies with comparison groups. We defined component therapy as combinations of apheresis platelets (aPLT), packed red blood cells, fresh frozen plasma, and fresh whole blood. We excluded case reports, opinion pieces, review articles, and studies involving non-human subjects. We did not include abstracts. As resuscitation practices changed dramatically with the advent of damage control resuscitation, we also excluded studies published before 2007.^{11–13} There was no language limitation. We included studies from both civilian and military settings.

The lead investigator (EC) identified relevant studies through a review of titles and abstracts against the exclusion criteria. Two different appraisers (EC, HEW) completed a full-text review of all potentially relevant studies to confirm study inclusion. Using the Newcastle-Ottawa Scale for non-randomized cohort studies, the reviewers appraised the quality of each selected study.¹⁴ The Newcastle-Ottawa

Scale awards “stars,” for methodological quality. A third reviewer (SD) resolved discrepancies.

To ensure consistency in the quality review, the reviewers aligned the interpretation of the Newcastle-Ottawa Scale score among the candidate studies.¹⁴ For representativeness, if a study included civilian patients, we considered the study to be “truly representative of the average trauma in the community.” If a study involved military trauma, the study was considered “somewhat representative of the average trauma in the community.” If the female population was disproportionately under-represented, we classified the study as “somewhat representative of the average trauma in the community.” For ascertainment of exposure, we accepted trauma registries as “secure records.” For “demonstration that outcome of interest was not present at the start of the study,” we assigned all studies as “yes.” For comparability, we assigned 1 star if a study controlled for 1 factor, 2 stars if the study controlled for > 1 factor, and 0 stars if there was no adjustment. For assessment of outcome, we accepted trauma registries as “independent blind assessment.” Finally, we assumed that all studies had adequate follow-up long enough for outcomes to occur.

2.3 | Data extraction

Three reviewers (EC, HW, and SD) extracted data from the identified papers. We extracted data from each of the identified papers. Data extracted included study design, setting, transfusion quantity, criteria for transfusion, mean/median age of patients, and percent male sex of the population. We also collected data on the types of blood products used in both intervention and control groups, the leukoreduction status of the products, and the titer levels in low titer type O whole blood interventions. Data concerning patient outcomes included 24-hour mortality, in-hospital mortality, and 30-day mortality. We extracted data including the type of statistical analyses and the adjustments used for confounders in each study. Any discrepancies were discussed and resolved by the reviewers.

2.4 | Data synthesis

The analysis focused on 2 primary outcomes: (1) 24-hour mortality and (2) in-hospital or 30-day mortality. We included early mortality because it is increasingly recognized to reflect efficacy of hemostatic interventions, and 24-hour mortality is reported in at least some of the studies published to date.¹⁵ We defined 24-hour mortality as death occurring within 24 hours of admission to the hospital. In-hospital mortality included deaths occurring during hospitalization. We defined 30-day mortality as death occurring within 30 days of hospitalization, or during hospitalization. This combined outcome was used because some papers specifically reported 30-day mortality, whereas others reported in-hospital mortality.

The Bottom Line

The use of whole blood instead of balanced component therapy during massive transfusion following trauma has been increasing. This meta-analysis of current studies demonstrates no difference in outcomes when whole blood is used, but it is limited by the small number of existing studies and significant heterogeneity of those studies.

2.5 | Data analysis

To test for heterogeneity among reported odds ratios (ORs), we calculated I^2 and tested its significance. We considered studies with I^2 values of < 25%, 25%–75%, and > 75% to represent low, moderate, and high heterogeneity, respectively. Chi-square tests of heterogeneity with a P -value < 0.05 were considered to represent heterogeneity higher than expected due to chance, and reason to fit a random effects meta-analysis of the log ORs. We used the Harbord's test to determine the risk of publication bias for both 24-hour and in-hospital/30-day mortality, separately, despite a small sample size for the former.¹⁶ Where available, we used adjusted outcomes reported by the original studies, converting all results into ORs. We calculated pooled estimates of ORs for both 24-hour and in-hospital/30-day death, by fitting a fixed or random effects meta-analysis model.¹⁷ We carried out this analysis using Stata v.15.0 (Stata, Inc., College Station, TX).

3 | RESULTS

3.1 | Systematic review

Of the 1759 citations identified in the search, 12 studies (reporting on 8431 patients) met the eligibility criteria of the systematic review (Figure 1; Table 1). All studies were available in English. The types of studies consisted of retrospective cohort ($n = 10$), prospective cohort ($n = 1$), and randomized control trial ($n = 1$). The majority of the studies originated from the civilian setting ($n = 7$). Of the civilian studies, most were conducted at institutions in the United States ($n = 6$). The remaining studies used data from military settings in either Afghanistan or Iraq. All of the studies involved mostly male patients (range = 72.7%–100%), and the mean age of patients ranged from 24–50.6 years.

Some studies included only patients receiving massive transfusion (≥ 10 U or red cells over 24 hours), while others included those receiving ≥ 1 U of red blood cells, over any period of time. There was significant variation in the definition of whole blood resuscitation. The types of whole blood in the intervention groups varied from low titer cold stored O-negative whole blood ($n = 2$), fresh whole blood ($n = 1$), unrefrigerated young whole blood ($n = 1$), and unspecified whole blood ($n = 1$) to combinations of whole blood with component therapy ($n = 7$).

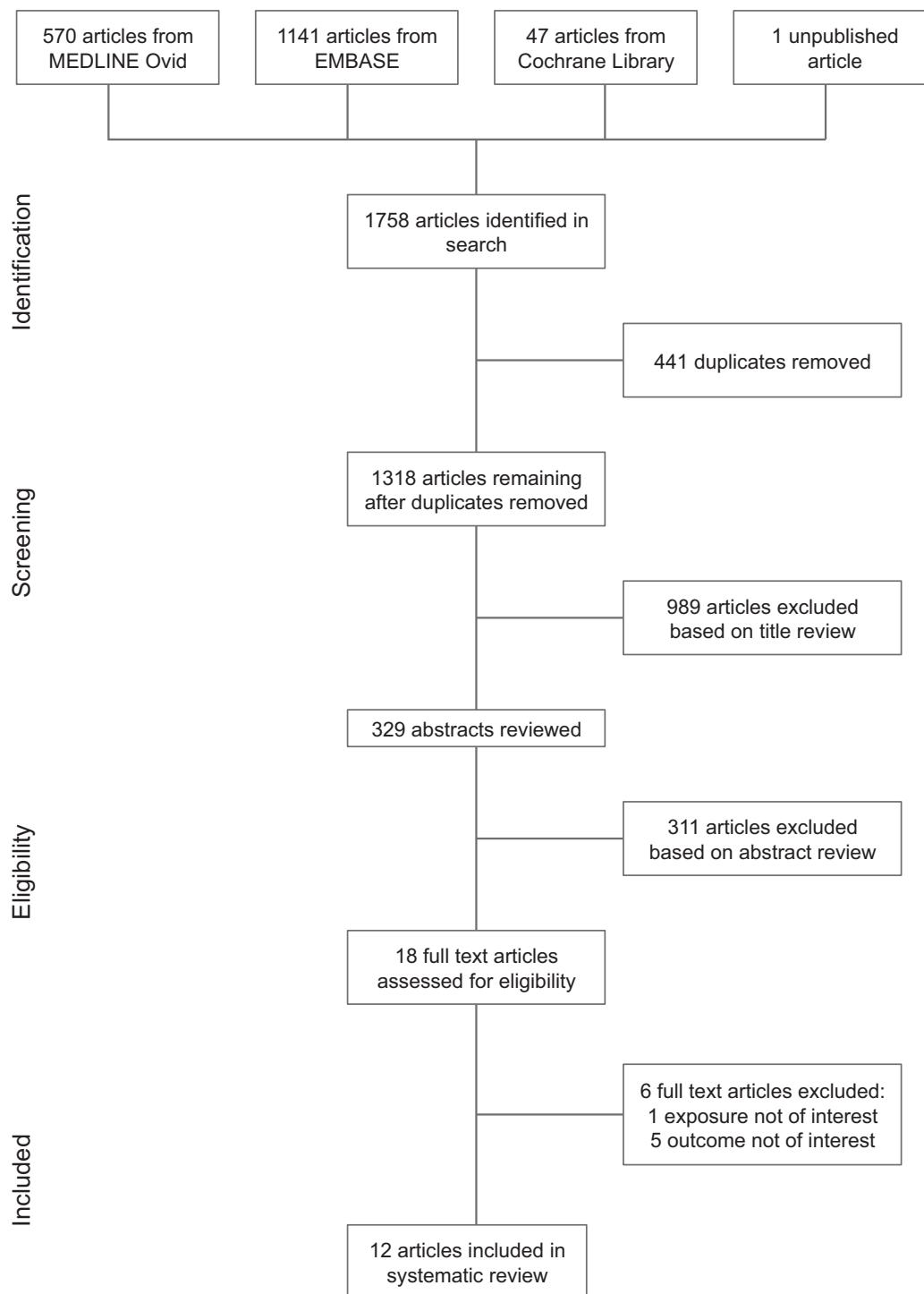


FIGURE 1 PRISMA flow diagram indicating study selection. *The unpublished article²⁰ was brought to attention of the reviewers by its authors

The latter combinations included fresh whole blood or warm fresh whole blood with component therapy, modified whole blood (mWB) with platelets, fresh whole blood or warm fresh whole blood with packed red blood cells and fresh frozen plasma, and low titer type O whole blood with CT.

Of the 7 studies conducted in the civilian setting, 4 reported on the use of low titer O-negative whole blood.¹⁸⁻²¹ The study by Williams et al²¹ was the only prospective cohort study. The Seheult et al¹⁸ and

Yazer et al¹⁹ articles compared low titer O-negative whole blood, or low titer O-negative whole blood with component therapy, to patients receiving component therapy alone. Zhu et al²⁰ compared low titer O-negative whole blood and component therapy in massively transfused patients without statistical analysis. The Cotton et al⁸ study comparing modified whole blood with platelets to packed red blood cells with fresh frozen plasma and platelets was the only randomized controlled trial identified. However, their study was a single center pilot,

feasibility trial, and not powered to detect differences in mortality. Ho et al²² used unrefrigerated young whole blood as the intervention of interest in massively transfused patients. Jones et al²³ conducted a National Trauma Data Bank analysis, using the ICD9 code 99.03 for “Other transfusion of whole blood” to identify civilian patients in the intervention group. The study compared these patients to those receiving component therapies using a multivariable logistic regression.

The studies conducted in the military setting included Auten et al,²⁴ Keneally et al,²⁵ Nessen et al,²⁶ Perkins et al,²⁷ and Spinella et al.²⁸ Auten et al,²⁴ Keneally et al,²⁵ Nessen et al,²⁶ and Spinella et al.²⁸ reported on the use of either fresh whole blood or warm fresh whole blood in combination with component therapy as an intervention. The Auten et al,²⁴ Keneally et al,²⁵ and Nessen et al²⁶ studies performed a propensity score adjusted logistic regression analysis, whereas Spinella et al.²⁸ compared cohorts via a multivariable logistic regression. Both

the Auten et al²⁴ and Perkins et al²⁷ studies examined patients undergoing massive transfusion; however, Perkins et al²⁷ compared the fresh whole blood cohort to patients receiving red blood cells, plasma, and apheresis platelets. Based upon the Newcastle Ottawa Scale, 10 studies were rated as “good” and 2 as “poor.”

3.2 | Meta-analysis

There were 5 studies that reported 24-hour mortality and 12 studies that reported in-hospital/30-day mortality. Harbord's test revealed no significant publication bias for either 24-hour mortality ($P = 0.82$) or in-hospital/30-day mortality ($P = 0.18$) (Figure 2).¹⁶ For 24-hour mortality, there was a small to moderate level of heterogeneity ($I^2 = 27.2\%$, $P = 0.37$) (Figure 2). The fixed effects pooled OR for 24-hour mortal-

TABLE 1 Characteristics of studies included in the systematic review and meta-analysis

Source	Design	Setting	Population	Intervention		Comparison/control		Intervention characteristics			
				Description	n	Description	n	Age	Male sex (%)	Leuko-reduction	Titer (anti-A & B)
Williams et al ²¹	Prospec. Observ.	US, civilian	Transfusion ≥ 1 U	LTO-WB	198	RBC and/or FFP	152	42 (26, 56)	72	No	<200
Zhu et al ²⁰	Retrospec. cohort	US, civilian	MT	LTO-WB	25	CT	175	–	–	No	<256
Seheult et al ¹⁸	Retrospec. cohort	US, civilian	Transfusion ≥ 1 U	LTO-WB or LTO-WB + CT	135	CT	135	40 (26, 61)	95.6	Yes	<50
Yazer et al ¹⁹	Retrospec. cohort	US, civilian	Transfusion ≥ 1 U	LTO-WB or LTO-WB + CT	47	CT	145	31 (18, 90)	100	Yes	<100
Auten et al ²⁴	Retrospec. cohort	Afghan., military	MT, ISS ≥ 15	FWB + CT	26	CT	35	24 $\pm$ 3.5	100	No	–
Keneally et al ²⁵	Retrospec. cohort	Afghan., Iraq, military	Transfusion ≥ 1 U, CRTT	WFWB + CT	281	CT	3656	24 (1, 77)	92 ^a	No	–
Jones et al ²³	Retrospec. cohort	US, civilian	Transfusion ≥ 1 U, ISS ≥ 25	WB	83	CT	1662	27 $\pm$ 8	83	–	–
Cotton et al ⁸	RCT	US, civilian	Transfusion ≤ 4 U 1 h, Level 1 trauma	mWB + PLT (6:1)	55	pRBC + FFP + PLT (6:6:1)	52	40 (29, 56) ^a	78	Yes	–
Nessen et al ²⁶	Retrospec. cohort	Afghan., military	Transfusion ≥ 1 U	FWB + pRBC + FFP	94	pRBC + FFP	394	28.1 $\pm$ 9.7	95.7	No	–
Ho et al ²²	Retrospec. cohort	Australia, civilian	MT	UYWB	77	CT	276	50.6 $\pm$ 19	72.7	No	–
Perkins et al ²⁷	Retrospec. Cohort	Iraq, military	MT	FWB	85	aPLT	284	27.6 $\pm$ 7.6	96.5	No	–
Spinella et al ²⁸	Retrospec. cohort	Afghan., Iraq, military	Transfusion ≥ 1 U	WFWB + pRBC + FFP	100	CT	254	24 (21, 29)	–	No	–

(continues)

TABLE 1 (Continued)

Analysis, adjustments		Outcome (mortality)						Newcastle-Ottawa scale appraisal			
		24 h		30 d		In-hospital		Selection	Comparability	Outcome	Total
		Interv.	Comp.	Interv.	Comp.	Interv.	Comp.				
Williams et al ²¹	MLR: age, AIS, SBP, arrival pH, MI	–	–	53/198	39/152	–	–	****	**	**	8
Zhu et al ²⁰	None	–	–	–	–	Sep-25	100/175	***	0	**	5
Seheult et al ¹⁸	Chi-square or Fisher exact test	12/135	17/135	–	–	25/135	33/135	****	**	**	8
Yazer et al ¹⁹	Chi-square or Fisher exact test	–	–	–	–	17/47	40/145	****	*	**	7
Auten et al ²⁴	LR, propensity score	Jan-26	Feb-35	Feb-26	Feb-35	–	–	***	**	***	8
Keneally et al ²⁵	LR, propensity score	–	–	–	–	60/281	468/3656	***	**	**	7
Jones et al ²³	MLR: age, sex, ISS, EMS TT, TT	–	–	–	–	17/83	429/1662	****	**	**	8
Cotton et al ⁸	Chi-square or Fisher exact test	11/55 ^b	10/52 ^b	22/55 ^b	14/52 ^b	–	–	–	–	–	–
Nessen et al ²⁶	LR, propensity score	–	–	–	–	May-94	35/394	****	*	***	8
Ho et al ²²	Cox regression, propensity score	–	–	–	–	31/77	97/276	****	**	***	9
Perkins et al ²⁷	Cox regression and MLR	16/85	45/284	29/68	71/177	–	–	****	**	**	8
Spinella et al ²⁸	MLR: sRBC, plasma, aPLT, WFWB, cryo., MT, rFVIIa use, plasma:RBC, PLT:RBC, anti-coag./add. vol.	4/100	31/254	5/100	45/254	–	–	****	**	**	8

aPLT, apheresis platelets; CRTT, combat related thoracic trauma; CT, component therapy; FFP, fresh frozen plasma; FWB, fresh whole blood; LTO-WB, low-titer group o-negative whole blood; MT, massive transfusion; mWB, modified whole blood; PLT, platelets; pRBC, packed red blood cells; UYWB, unrefrigerated young whole blood; WFWB, warm FWB; Cryo., cryoprecipitate; EMS TT, EMS transfer time; LR, logistic regression; MI, mechanism of injury; MLR, multivariable logistic regression; rFVIIa, recombinant factor VIIa; SBP, systolic blood pressure; sRBC, stored RBC; TT, transfusion type.

Contiguous variables reported as mean $\pm$ SD or median (IQR)

^aIndicates data for total patients in the study.

^bIndicates intent-to-treat analysis data.

*, **, ***, **** denote ratings on the Ottawa-Newcastle Scale.

ity was 0.83 (95% confidence [CI] = 0.56–1.24). For in-hospital/30-day mortality, there was a moderate to high degree of heterogeneity ($I^2 = 87.3\%$, $P = 0.37$) (Figure 3). The DerSimonian and Laird random effects pooled OR for in-hospital/30-day mortality was 0.79 (95% CI = 0.49–1.31).¹⁷

4 | LIMITATIONS

Our study has limitations. Even with a comprehensive search strategy using multiple databases, we may have failed to identify appropriate studies. The included studies were largely retrospective or observational, with only 1 small randomized trial, and the techniques for multivariable adjustment varied. The results of observational studies may be influenced by confounders. However, while observational studies have important limitations, they represent the best data available,

and we therefore believe their inclusion to be justifiable.^{29,30} Many of the studies took place in the military setting, encompassing primarily males with penetrating trauma. The applicability of these studies to civilian trauma may be limited as the latter includes a larger portion of blunt trauma patients, with different demographics and types of whole blood. The definition of whole blood also varied widely across studies. Only 5 studies contributed to the meta-analysis of 24-hour mortality. The results of the meta-analysis were influenced primarily by 2 studies. We did not search clinical trial registries for additional trials.

5 | DISCUSSION

Our systematic review and meta-analysis of 12 studies of whole blood resuscitation in trauma revealed wide heterogeneity in study design, methods, setting, population, interventions, and outcomes. The most

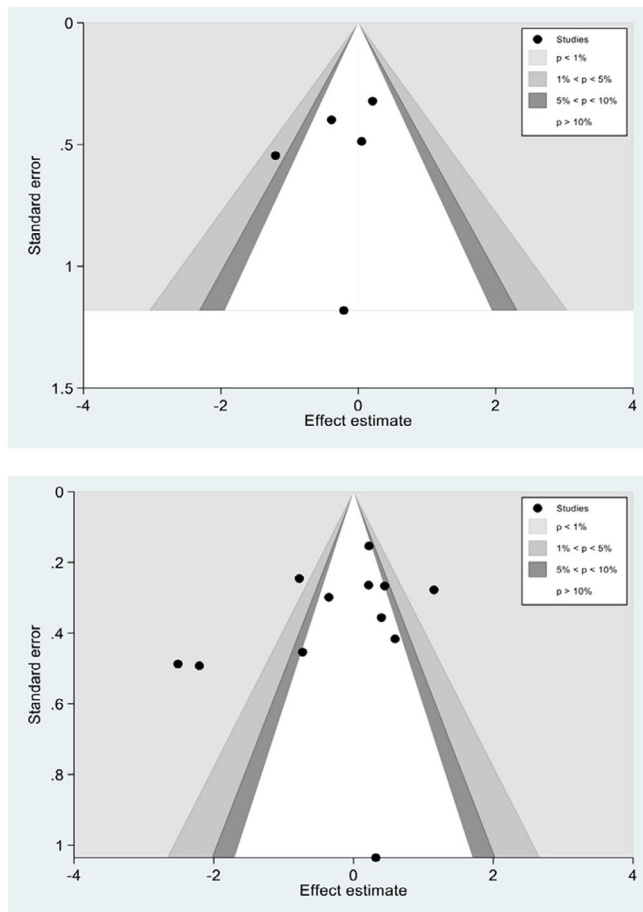


FIGURE 2 Funnel plots for 24-hour mortality (upper) and in-hospital/30-day mortality (lower pane). *P*-values reflect results of Harbord's test

striking observation was that the type of whole blood used in each study varied widely, ranging from the fresh warm blood used in military settings to cold stored blood O+ or O- used in civilian studies, either leukoreduced or not. The definition of whole blood treatment also varied, with some studies classifying whole blood groups as patients receiving exclusively whole blood and others mixtures of whole blood with other blood product components. Other notable differences included the study setting (military vs civilian) and endpoints (24-hour, hospital and 30-day mortality).

Given the extent of heterogeneity across studies, some would consider a meta-analysis to be inappropriate. However, we feel that the analysis is helpful for illuminating the limitations of the existing literature. For example, the forest plots are useful for visualizing the range of outcomes and the potential pooled effect across the 12 studies. However, we emphasize that, given the limitations of the primary studies, readers should resist from making formal inferences from these data. Rather, they should use the current review as the basis for understanding the limitations of existing data and to guide future research. Given the substantial limitations of observational studies in this population, randomization in a prospective clinical trial is likely the best approach to determining the effectiveness of whole blood therapy. Our review highlights important design considerations for conducting such a trial.

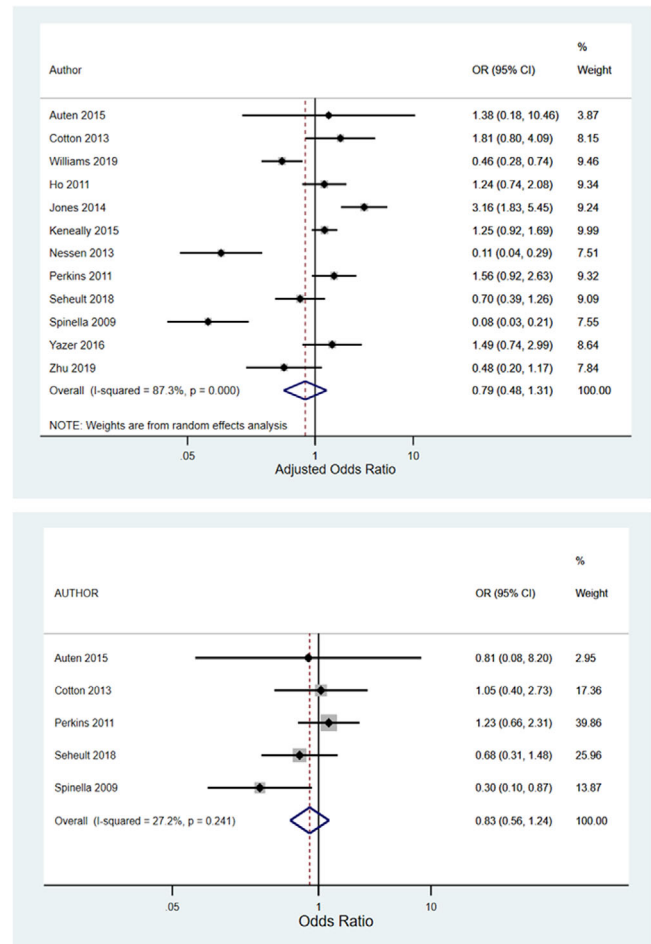


FIGURE 3 Forest plots illustrating random effects meta-analyses of the associations between whole blood transfusion and 24-hour mortality (upper pane) and in-hospital/30-day mortality (lower pane)

If the objective is to evaluate whole blood in civilian trauma, then the trial should take place in trauma systems currently using whole blood, the selection of patients should include both blunt and penetrating trauma patients as well as females of child-bearing age. Studies must identify whole blood transfusion practices, including the types of whole blood used, the application of leukoreduction and methods of storage. The minimum quantity of whole blood transfused that constitutes the whole blood group should be agreed upon, including the type and number of components allowed before receiving whole blood. Study endpoints might include not just hospital mortality but also early mortality or physiologic measures such as thromboelastography.^{15,31} Because trials of acute therapies may require large sample sizes, innovative trial designs using adaptive and Bayesian techniques might be considered to increase trial efficiency and make the results more interpretable.³²

Although not directly addressed by this systematic review, an important factor influencing the current use of whole blood involves the logistics of trauma blood transfusion; that is, it is simpler to give a single unit of whole blood rather than separate units of red cells, plasma, and platelets. In certain settings, the preparation and storage of whole blood may be less costly than similar amounts of component therapy, and the handling of fewer blood products may be less prone

to administrative error.³³ Thus, cost-effectiveness and logistical burden may represent important outcomes in a prospective study or trial. In conclusion, there is wide heterogeneity in the design, setting, interventions, and outcomes of published studies of whole blood resuscitation. Additional study is needed to determine the effectiveness of whole blood.

AUTHOR CONTRIBUTIONS

HEW, SMD, JOJ, and EC conceived the study. HEW, SMD, and JOJ designed the study. EC, HEW, JOJ, and SMD collected the data and reviewed the articles. AB and SMD conducted the statistical analysis. All authors contributed to the critical review of analytic results. EC drafted the paper. All authors contributed to the critical review and revision of the paper. EC and HEW take overall responsibility for the paper.

CONFLICT OF INTEREST

Dr. Michael Blaivas was the supervising editor for the final review process of this paper. Dr. Wang did not participate in the review process or editorial decision to publish the paper.

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APPENDIX 1:

Publication search strategy

1. Blood transfusion.ti,ab,kw. or exp Blood Transfusion/
2. exp Hemorrhage/ or (haemorrhag*.mp. or hemorrhag*).ti,ab,kw.
3. hemorrhagic shock.ti,ab,kw. or exp Shock, Hemorrhagic/
4. ("Injur* and Wound*" or "Wound* and Injur*" or Wound* Injur* or Trauma* or Injur* Wound* or Injur* or Wound*).ti,ab,kw.
5. wounds.ti,ab,kw. or exp "Wounds and Injuries"/
6. (Personnel Military or Armed Forces Personnel of Personnel Armed Forces or Military or Air Force Personnel or Force Personnel Air or Personnel Air Force or Army Personnel or Personnel Army or Submarine* or Marine* or Navy Personnel or Personnel Navy or Sailor* or Soldier* or Military Deployment* or Deployment* Military or Coast Guard).ti,ab,kw.
7. military personnel.ti,ab,kw. or exp Military Personnel/
8. exp Resuscitation/ or resuscitation.ti,ab,kw.
9. blood preservation.ti,ab,kw. or exp Blood Preservation/
10. warfare.ti,ab,kw. or exp Warfare/
11. 1 and (2 or 3)
12. 1 and (4 or 5)
13. 1 and (6 or 7)
14. 1 and 8
15. 1 and 9
16. 1 and 10
17. (6 or 7) and 10
18. 8 and (4 or 5)
19. 8 and 9
20. 9 and (4 or 5)
21. whole blood.mp.
22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 10 or 20
23. 21 and 22