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Research Article

The Impact of LTOWB *vs.* Standard Component Therapy on Transfusion-Related Complications in Trauma Resuscitation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Haemorrhage secondary to trauma is the leading cause of preventable fatalities. Low Titre O Whole Blood (LTOWB) has been reintroduced as a significant alternative to Component Therapy (CT), in trauma resuscitation due to its balanced composition. This systematic review and meta-analysis compares the incidence of transfusion related complications, including Pulmonary Embolism (PE), Deep Vein Thrombosis (DVT), Acute Kidney Injury (AKI) and Acute Respiratory Distress Syndrome (ARDS), in trauma patients receiving LTOWB *versus* CT.

Methods: A search of PubMed, Scopus, Embase and Web of Science databases was conducted to identify studies reporting adverse outcomes in adult civilian trauma patients receiving LTOWB or CT. Eligible studies were assessed for quality using the STROBE checklist. Meta-analyses were performed using RevMan software (Version 8.5.2, The Cochrane Collaboration, UK) to calculate pooled Odds Ratios (ORs) with 95% Confidence Intervals (CI) for PE, DVT, AKI and ARDS.

Results: Ten studies met the inclusion criteria. No statistically significant differences were observed between LTOWB and CT groups for PE (OR: 1.17, 95% CI, 0.73-1.89, p=0.51), DVT (OR: 0.83, 95% CI, 0.47-1.45, p=0.51), AKI (OR: 1.37, 95% CI, 0.77-2.44, p=0.28), or ARDS (OR: 1.35, 95% CI, 0.84-2.17, p=0.21). Moderate heterogeneity was observed for some outcomes.

Conclusion: LTOWB offers a viable alternative to CT in trauma resuscitation without increasing the risk of transfusion related adverse outcomes. Further randomised controlled trials with standardised criteria are required to confirm LTOWB's safety and its role in reducing adverse outcomes.

Keywords: LTOWB; Whole blood; Component therapy; Pulmonary embolism; Deep vein thrombosis; Acute kidney injury; Acute respiratory distress syndrome

Abbreviations: LTOWB: Low Titre O Whole Blood; CT: Component Therapy; PE: Pulmonary Embolism; DVT: Deep Vein Thrombosis; AKI: Acute Kidney Injury; ARDS: Acute Respiratory Distress Syndrome

INTRODUCTION

Exsanguination secondary to traumatic injury is the leading cause of preventable fatalities among civilian and military trauma patients [1,2]. Severely bleeding patients are at risk of falling into the lethal triad of coagulopathy, hypothermia and metabolic acidosis [3]. The current literature documents that early intervention and a balanced approach to resuscitation is significant in preventing early coagulopathy and the lethal triad [4-6]. The current Damage Control Resuscitation (DCR) recommendation includes product administration in a 1:1:1 ratio (1 unit Red Blood Cell (RBC), 1 unit Fresh Frozen Plasma (FFP), 1 unit platelets), for prevention of early trauma-induced coagulopathy [3]. Effectively, the DCR approach aims to replace patient blood loss with an approximate whole blood transfusion [3]. It is with this recommendation that historic whole blood transfusion practices are being revisited in a modern way.

LTOWB (Low Titre Group O Whole Blood)

LTOWB contains all the components of whole blood (RBC, plasma and platelets), essentially providing the balanced approach, per each

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unit. The history of whole blood transfusions dates to the early 1900s-1940s, with documented transfusions of whole blood during World War I (WWI) and World War II (WWII), continuing into the Vietnam War [7]. During the 1960s-1970s, fractionated blood components became more popular due to scientific advancements in product collection and storage [7]. Despite improvements in trauma resuscitation methods, pre-hospital haemorrhage is still the leading cause of death in military patients [2]. To provide balanced DCR in the austere environments of the Iraq and Afghanistan war, whole blood transfusion was reintroduced with high reported success rates [8]. This documented success has led to the implementation of LTOWB in trauma resuscitation of civilians. LTOWB is whole blood collected from donors (typically male) who have low titres of Immunoglobulin M (IgM) anti-A and anti-B, stored for up to 21 days [9]. According to the Association for the Advancement of Blood and Biotherapies (AABB) standard 5.27.2, the definition of "low titre" must be defined by the institution, with products from <1:50 to <1:256 [10].

Clinical significance

The time from traumatic injury to initial blood transfusion is significant, with studies showing improved mortality rates with earlier intervention [5,6]. The use of LTOWB in trauma settings can reduce the quantity of products transfused as the 1:1:1 ratio is contained in a single unit, as opposed to standard CT [11]. Balanced resuscitation through CT includes blood products which are stored at different temperatures and require different preparation, significantly increasing the logistical efforts to ensure timely transfusion. In CT, there is increased transfusion of fluids lacking haemostatic and oxygen-carrying properties (anticoagulants and preservatives) [12]. Due to the processing of CT products the haematocrit, platelets and coagulation factors are also decreased [13]. Lastly, it has been reported that LTOWB could be more cost effective when implemented in addition to CT [14]. It is these factors which highlight the valid role LTOWB can play in DCR, with potential to simplify transfusion protocols while providing balanced resuscitation over less units.

Transfusion-related complications

PE and DVT: The reported incidence of PE in trauma patients is 0.11% to 2.3% [15]. While the reported incidence of DVT in trauma patients varies, it well documented that DVT is a common trauma-associated complication [16]. The risk of Venous Thromboembolic (VTE) events increase where there is damage of the vessel wall, turbulent blood flow or hypercoagulability, collectively known as Virchow's Triad [16]. It has been reported several times in the literature that blood transfusion increases the likelihood of experiencing a VTE event [17-19]. While the influence of RBC transfusion in VTE development is not entirely understood, it is known that a hypercoagulable state secondary to traumatic injury predisposes one to acute VTE events [20].

Acute Kidney Injury (AKI): AKI, previously known as acute renal failure, results from many aetiological causes leading to a sudden and typically reversible decline in glomerular function [21]. In patients presenting with haemorrhagic shock, there is a 43% risk of developing AKI [22]. It has been reported that transfusion can lead to AKI through mechanism of haemolysed RBC increasing the free haemoglobin, iron and pro-inflammatory molecules leading to glomerular damage and compromising kidney function [23].

Acute Respiratory Distress Syndrome (ARDS): ARDS is a severe inflammatory lung condition often affecting critically ill patients and has a grave prognosis [24]. There are many risk factors associated with the development of ARDS, with RBC transfusions having been reported to increase its risk [24]. The reported incidence of ARDS in trauma patients is 8.4% [25]. The exact pathophysiology is complex and disputed. It is believed that RBC transfusion promotes pro-inflammatory cascades, in conjunction with increased vascular permeability and leukocyte activation leading to capillary endothelial injury and diffuse alveolar damage [26].

Scope of the review

Current literature compares the outcomes between patients receiving LTOWB and/or CT as part of their resuscitation. The major parameters covered include mortality rates (4-24 h, 28-30 days), transfusion volumes, Intensive Care Unit (ICU), Length of Stay (LOS), hospital LOS and an overall mention of complications [27-29]. As research in this area continues to expand, there is a need for a systematic review and meta-analysis to assess the incidence of transfusion related complications in adult civilian trauma patients who received LTOWB *versus* CT.

This systematic review and meta-analysis aims to evaluate the incidence of certain transfusion-related complications in adult civilian trauma patients following transfusion of LTOWB or CT during trauma resuscitation. This review will compare LTOWB against standard CT to determine whether transfusion of LTOWB leads to a reduction in complications such as PE, DVT, AKI or ARDS, in trauma settings. By elucidating the significant benefits of LTOWB over CT, this review can influence considerations towards which products are most appropriate for use in trauma resuscitation by optimising transfusion protocols, reducing transfusion-related complications and improving patient safety.

Primary objective

The primary research question for this study was formulated in accordance with the Patient or Problem, Intervention, Comparison and Outcome (PICO) framework [30]. In civilian trauma patients requiring transfusion as part of resuscitation (population), does the use of LTOWB (intervention) reduce transfusion-related complications (outcome) when compared to standard CT (comparison)? This study aims to systematically address this research question by comparing the incidence of adverse events (PE, DVT, AKI or ARDS), following transfusion with LTOWB *versus* CT.

MATERIALS AND METHODS

Study design

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines to gather relevant articles investigating the incidence of adverse complications in trauma patients receiving LTOWB or CT therapy as part of their resuscitation [31].

Search strategy

To identify relevant literature, searches were conducted through PubMed, Scopus, Embase and Web of Science databases, without publication date restrictions. Key search terms included "LTOWB", "low titer/titre O whole blood", "whole blood", "whole blood resuscitation", "whole blood transfusion" AND "trauma" and "whole blood" AND "resuscitation" AND "trauma". To ensure full coverage, both British and American spelling of 'titre'and 'titer' were included where relevant. No articles were added by manual search. Articles retrieved from database searches were saved into EndNote.

Eligibility criteria

EndNote was used to remove duplicates and organise articles for eligibility assessment. Articles were excluded based on title and abstract, then assessed for eligibility. Articles which examined the adverse outcomes (PE, DVT, AKI, ARDS), following transfusion with LTOWB or CT in adult (≥ 16 years) civilian trauma patients were considered eligible. Articles were excluded if they were:

- Irrelevant to the research question,
- Case studies,
- Systematic review, meta-analyses or review,
- Obstetrics/paediatrics,
- Lacked control group (CT therapy only) and
- Lacked specification of LTOWB product.

Assessment of methodology quality

The eligible studies were assessed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for their methodological quality [32].

Data extraction and management

Data was extracted from the eligible studies, including the primary author, study design, country of publishing, study period, sample size and the incidence of the parameters measured for analysis. The selected parameters included PE, DVT, AKI and ARDS.

Statistical analysis

To conduct the meta-analysis, Review Manager (RevMan) software (Version 8.5.2, The Cochrane Collaboration, UK) was accessed *via* the Cochrane website [33]. A two-way proportion analysis was used for the incidence of PE, DVT, AKI and ARDS in LTOWB *versus* CT groups. Each analysis used the Mantel-Haenszel statistical method to calculate Odds Ratio (OR) using random effects model. The results for each parameter were represented visually in forest plots. RevMan software determined the overall P-value to evaluate the statistical significance, 95% Confidence Interval (CI), I^2 to assess study heterogeneity (het.), including the associated het. p-value. A p-value of <0.05 was deemed statistically significant.

RESULTS

Study selection

As shown in Figure 1, the search strategy identified 5,474 articles through PubMed, Scopus, Embase and Web of Science databases. The search results were extracted and imported into EndNote for filtering and duplicate removal. Of the 5,474 articles, 3,000 were duplicates, 1,777 were excluded based on title irrelevancy and a further 477 were excluded based on abstract irrelevancy. The remaining 191 articles were screened *via* full-text reading to determine their eligibility. In total, 10 articles were accepted through the screening process and no additional eligible articles were identified through manual reference checks.

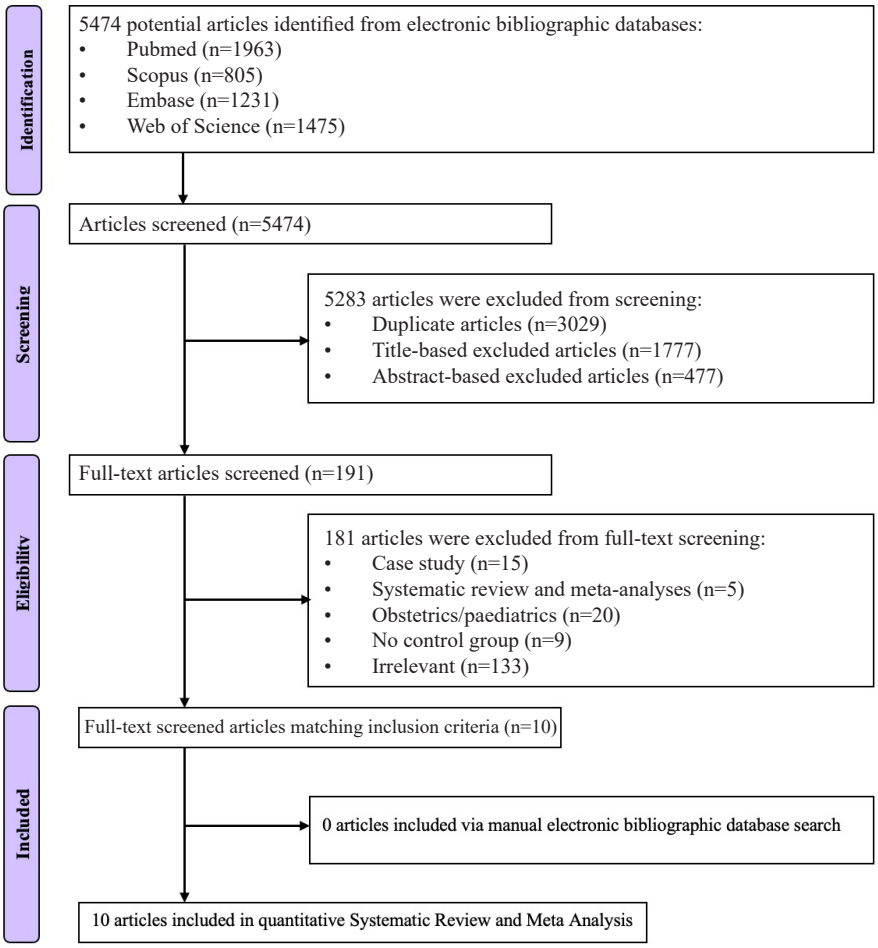

Figure 1: Overview of study selection according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Guidelines for Systematic Review on risk of PE, DVT, AKI and ARDS following transfusion with LTOWB or CT in civilian trauma patients [31].

Study characteristics

As shown in Table 1, the 10 articles included in this meta-analysis identified the incidence of PE, DVT, AKI andARDS in patients who had either LTOWB or CT as part of their trauma resuscitation. The studies conducted in the United States of America (USA) between 2015 to 2021, were either prospective [35-38,40,42] or retrospective [36,39,41,43]. The sample size included adult (≥ 16 years) civilian trauma patients who were monitored for adverse outcomes (PE, DVT, AKI or ARDS) following transfusion with LTOWB or CT during their resuscitation. Of the 10 articles, 8 included incidence of PE and DVT [34,35,37-40,42,43], 6 included AKI [35,36,38,39,41,43] and another 6 included ARDS [35-40]. The sample sizes ranged from 86 to 1617.

The data included in the meta-analysis is shown in Table 2. Categorical data were described as the number of adverse events occurring (count) out of the sample group (n). The table reports both the absolute counts and proportional rates of the incidence of adverse events, including PE, DVT, AKI and ARDS, comparing LTOWB and CT groups. The studies varied in sample sizes, ranging from smaller cohorts, such as Guyette et al. [37] with 86 patients, to larger ones, like Dilday et al., with 1,617 patients [35].

Table 1: Overview of eligible study characteristics and meta-analysis parameters.

Study	Year	Study design	Country	Study period	Sample size
Bohan et al. [34]	2021	Retrospective	USA	2018-2020	182
Dilday et al. [35]	2024	Prospective	USA	-	1617
Duchesne et al. [36]	2021	Prospective	USA	2019-2020	253
Guyette et al. [37]	2022	Prospective	USA	2018-2020	86
Hatton et al. [38]	2023	Prospective	USA	2017-2018	564
Lee et al. [39]	2022	Retrospective	USA	2019-2020	299
Niemann et al. [40]	2023	Prospective	USA	2018-2020	193
Seheult et al. [41]	2018	Retrospective	USA	2015-2017	252
Sperry et al. [42]	2023	Prospective	USA	2018-2021	1051
Yazer et al. [43]	2021	Retrospective	USA	2015-2019	252

Table 2: Summary of included study characteristics and adverse outcome incidence among LTOWB and CT groups.

Study	Year	PE	DVT	ARDS	AKI/ARF
Bohan et al. [34]	2021	LTOWB: 3/87 CT: 2/95	LTOWB: 3/87 CT: 1/95	-	-
Dilday et al. [35]	2024	LTOWB: 26/1199	LTOWB: 69/1199	LTOWB: 36/1199	LTOWB: 185/1199
		CT: 13/418	CT: 20/418	CT: 6/418	CT: 28/418
Duchesne et al. [36]	2021	-	-	LTOWB: 0/73 CT: 11/180	LTOWB: 3/73 CT: 17/180
Guyette et al. [37]	2022	LTOWB: 1/40 CT: 1/46	LTOWB: 1/40 CT: 3/46	LTOWB: 7/40 CT: 7/46	-
Hatton et al. [38]	2023	LTOWB: 8/341 CT: 6/223	LTOWB: 7/341 CT: 11/223	LTOWB: 24/341 CT: 13/223	LTOWB: 29/341 CT: 19/223
Lee et al. [39]	2022	LTOWB: 4/169 CT: 2/130	LTOWB: 4/169 CT: 6/130	LTOWB: 2/169 CT: 1/130	LTOWB: 8/169 CT: 6/130
Niemann et al. [40]	2023	LTOWB: 2/40 CT: 0/153	LTOWB: 1/40 CT: 2/153	LTOWB: 0/40 CT: 2/153	-
Seheult et al. [41]	2018	-	-	-	LTOWB: 25/126 CT: 18/126
Sperry et al. [42]	2023	LTOWB: 38/624 CT: 26/427	LTOWB: 49/624 CT: 22/427	-	-
Yazer et al. [43]	2021	LTOWB: 10/126 CT: 3/126	LTOWB: 4/126 CT: 12/126	-	LTOWB: 33/70* CT: 37/87*

Note: *39 CT and 56 LTOWB recipients did not have any blood culture results during the first 7 days.
Abbreviations: n: Sample Size; PE: Pulmonary Embolism; DVT; Deep Vein Thrombosis; ARDS: Acute Respiratory Distress Syndrome; AKI: Acute Kidney Injury; ARF: Acute Renal Failure; LTOWB; Low Titre O Whole Blood; CT: Component Therapy.

Study quality assessment

The 10 included studies were individually assessed for quality using the STROBE checklist as shown in Table 3, [32]. Most of the selected STROBE criteria were fulfilled, indicating adequate reporting and methodology, supporting the inclusion of these studies as 'high quality'. Eligibility criteria was marked as partially fulfilled for some studies due to the absence of exclusion criteria [35,43]. Defined outcomes were also partially fulfilled for Seheult et al., as the outcomes were inferred but not explicitly stated in the methods section [41]. Major elements of the study design were not fulfilled for some studies, as the information was presented elsewhere [41,43].

META-ANALYSIS OF THE INCIDENCE OF ADVERSE OUTCOMES IN CIVILIAN TRAUMA PATIENTS

Incidence of PE

For the meta-analysis of PE incidence in trauma patients following resuscitation with LTOWB or CT, 8 studies were included, presented as a forest plot in Figure 2A, [34,35,37-40,42,43]. The overall incidence of PE was 3.63% in LTOWB and 3.39% in CT groups. The pooled OR was 1.17 (95% CI, 0.73 to 1.89, p-value=0.51), indicating no statistically significant difference between LTOWB and CT in the incidence of PE. The I^2 value of 27% (het. p-value=0.21) suggests moderate heterogeneity amongst studies. Selection biases (random sequence generation and allocation concealment) were prevalent in most included studies [34,35,39,43]. Additionally, performance bias (blinding of participants and personnel) was present in all included studies. Given the nature of trauma settings, it was unclear whether detection bias (blinding of outcome assessment) was adequately addressed or even relevant. Other biases included no titre or leukoreduction clarification [35,43].

Incidence of DVT

For the meta-analysis of DVT incidence in trauma patients following resuscitation with LTOWB or CT, 8 studies were included, presented as a forest plot in Figure 2B, [34,35,39-40,42,43]. The overall incidence of DVT was 5.55% in LTOWB and 5.00% in CT groups. The pooled OR was 0.83 (95% CI, 0.47 to 1.45, p-value=0.51), indicating no statistically significant difference between LTOWB and CT in the incidence of DVT. The I^2 value of 54% (het. p-value=0.03) suggests moderate heterogeneity amongst studies. Identical bias trends were seen for DVT as the included studies were the same. Other biases included no titre or leukoreduction clarification [35,43].

Incidence of AKI

For the meta-analysis of AKI incidence in trauma patients following resuscitation with LTOWB or CT, 6 studies were included, presented as a forest plot in Figure 2C, [35,36,38,39,41,43]. The overall incidence of AKI was 16.50% in LTOWB and 12.03% in CT groups. The pooled OR was 1.37 (95% CI, 0.77 to 2.44, p-value=0.28), indicating no statistically significant difference between LTOWB and CT in the incidence of AKI. The I^2 value of 70% (het. p-value=0.005) suggests high heterogeneity amongst studies. Selection biases (random sequence generation and allocation concealment) were prevalent in most included studies [35,39,41,43]. Performance bias (blinding of participants and personnel) was present in all included studies, given the nature of trauma settings. Other biases included no titre or leukoreduction clarification [35,36,43].

Incidence of ARDS

For the meta-analysis of ARDS incidence in trauma patients following resuscitation with LTOWB or CT, 6 studies were included, presented as a forest plot in Figure 2D [35-40]. The overall incidence of ARDS was 3.85% in LTOWB and 3.60% in CT groups. The pooled OR was 1.35 (95% CI, 0.84 to 2.17, p-value=0.21), indicating no statistically significant difference between LTOWB and CT in the incidence of ARDS. The I^2 value of 0% (het. p-value=0.43) suggests low heterogeneity amongst studies. Again, selection bias (random sequence generation and allocation concealment) was prevalent in most included studies [35,37,39]. Performance bias was seen in all included studies due to the unpredictable study environment. Other biases included no titre or leukoreduction clarification [35,36].

Table 3: Evaluation of eligible studies according to the (STROBE) checklist [32].

Study	Year	Introduction	Methods				Results	Discussion
		Explains the scientific background and rationale for study	Key elements of study design outlined	Eligibility criteria or matched criteria for selection of participants	Defines all outcomes	Describes statistical methods	Reports numbers of individuals at each stage of study and indicates any missing data for each variable	Summarises key results with discussion of limitations
Bohan et al. [34]	2021	Y	Y	Y	Y	Y	Y	Y
Dilday et al. [35]	2024	Y	Y	P[a]	Y	Y	Y	Y
Duchesne et al. [36]	2021	Y	Y	Y	Y	Y	Y	Y
Guyette et al. [37]	2022	Y	Y	Y	Y	Y	Y	Y
Hatton et al. [38]	2023	Y	Y	Y	Y	Y	Y	Y
Lee et al. [39]	2022	Y	Y	Y	Y	Y	Y	Y
Niemann et al. [40]	2023	Y	Y	Y	Y	Y	Y	Y
Seheult et al. [41]	2018	Y	N[b]	Y	P[c]	Y	Y	Y

Sperry et al. [42]	2023	Y	Y	Y	Y	Y	Y	Y
Yazer et al. [43]	2021	Y	N[b]	P[a]	Y	Y	Y	Y

Note: Y: Criteria fulfilled; P: Criteria partially fulfilled; N: Criteria not fulfilled; a: No exclusion criteria; b: Presented elsewhere; c: Outcomes inferred, not explicitly mentioned.

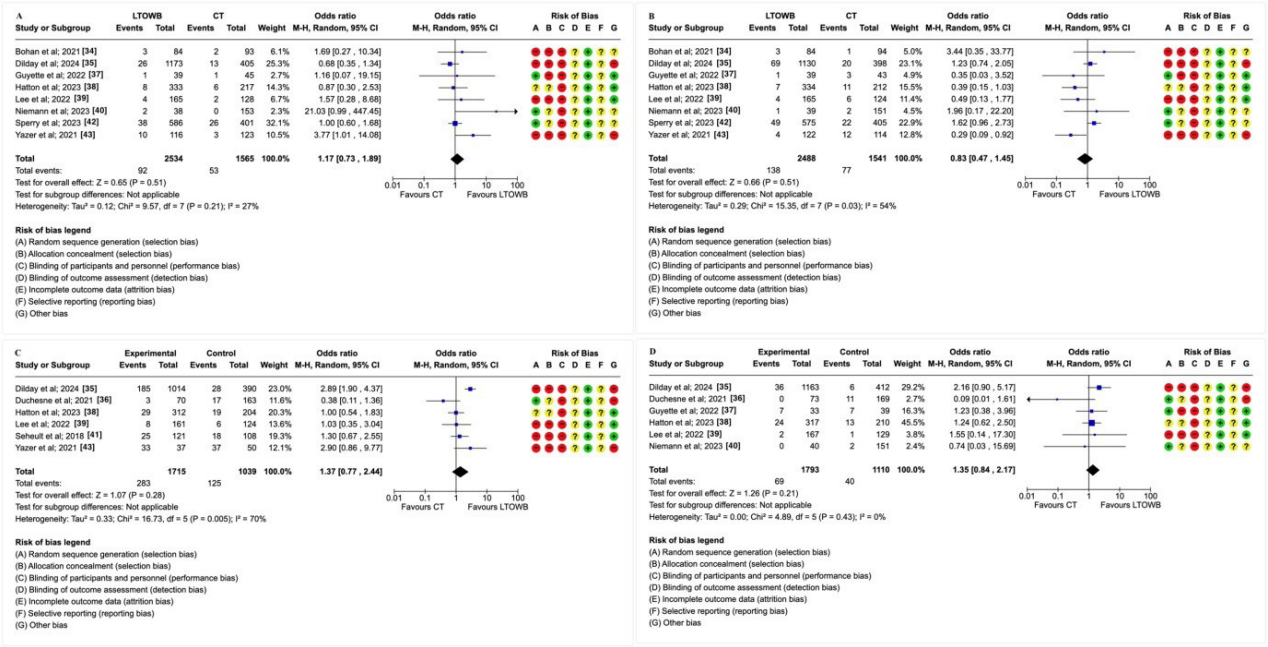

Figure 2: Forest plots of meta-analysis on proportions comparing incidence of adverse outcomes in Low Titre O Whole Blood (LTOWB) and Clotting Time (CT) groups. **Note:** A) Incidence of pulmonary embolism in LTOWB *vs.* CT groups; B) Incidence of deep vein thrombosis in LTOWB *vs.* CT groups; C) Incidence of acute kidney injury in LTOWB *vs.* CT groups; D) Incidence of acute respiratory distress syndrome in LTOWB *vs.* CT groups, were expressed using two-way proportion data with Mantel–Haenszel statistics to calculate odds ratio using random effects model. Statistical significance was evaluated by the overall p-value and heterogeneity was evaluated by I^2 and het. p-value. The weighting of each study was determined by its relative sample size.

DISCUSSION

This systematic review and meta-analysis aimed to evaluate if transfusion with LTOWB during initial trauma resuscitation would reduce adverse outcomes in comparison to standard CT, with a specific focus on incidence of PE, DVT, AKI and ARDS. The meta-analysis results revealed no statistically significant difference in the incidence of adverse outcomes between the groups transfused with LTOWB and those transfused with CT.

Pulmonary Embolism (PE)

The overall incidence of PE was 3.63% in LTOWB and 3.39% in CT groups (95% CI, 0.73 to 1.89, p=0.51), suggesting a non-significant trend toward increased risk of PE with LTOWB transfusion. Most studies showed similar findings except Niemann et al., who reported a significantly higher OR of 21.03 with a wide CI (95% CI, 0.99 to 447.45), which is an extreme outlier compared to the other studies with the average reported OR being closer to 1 [40]. The wide CI suggests substantial uncertainty in the estimate, likely due to the difference in sample size and low frequency of PE incidence. Dilday et al. and Niemann et al. contributed heavily to the analysis weight, which may have disproportionately influenced the pooled estimate [35,40]. There was moderate heterogeneity amongst studies (I^2=27%, het. p=0.21), however this was not statistically significant, suggesting the heterogeneity observed may be attributed to random variation rather than meaningful differences between the studies.

Deep Vein Thrombosis (DVT)

The overall incidence of DVT was 5.55% in LTOWB and 5.00% in CT groups (95% CI, 0.47 to 1.45, p=0.51), suggesting a non-significant trend toward increased risk of DVT with CT transfusion. The statistically significant heterogeneity score (I^2=54%, het. p=0.03) indicates that the variability in DVT outcomes across the studies is due to differences in diagnostic methods, patient populations, interventions or methodologies. Guyette et al., and Yazer et al., reported less associated risk of DVT development with transfusion of LTOWB with an OR of 0.29 (95% CI, 0.09 to 0.92) and 0.35 (95% CI, 0.03 to 3.52), respectively [37,43]. These studies may have contributed to the moderate heterogeneity, by swaying the estimate towards a lower risk for LTOWB. As with PE, the absence of statistical significance in DVT incidence suggests that LTOWB does not reduce the risk of VTE events, when compared to CT.

Acute Kidney Injury (AKI)

The overall incidence of AKI was 16.50% in LTOWB and 12.03% in CT groups (95% CI, 0.77 to 2.44, p=0.28), suggesting a non-significant trend toward increased risk of AKI with LTOWB transfusion. There is statistically significant heterogeneity amongst the included studies (I^2=70%, het. p=0.005), likely due the multifactorial causes of AKI as well as differences in study design, patient demographics or transfusion practices [21]. Dilday et al., and Yazer et al., stood out as outliers with reported OR of 2.89 (95% CI, 1.90 to 4.37) and 2.90

(95% CI, 0.86 to 9.77) respectively [35,43]. Both studies suggest a substantially increased risk of AKI development following transfusion with LTOWB, significantly inflating the pooled OR estimate. In contrast, Duchesne et al., reported an OR of 0.38 (95% CI, 0.11 to 1.36), indicating a lower risk of AKI development following LTOWB transfusion [36]. This discrepancy between studies highlights the significant heterogeneity score and indicates the need for further investigation into the underlying causes of such variation, as well as what considerations should be made around patient samples, study design and what confounders to eliminate.

Acute Respiratory Distress Syndrome (ARDS)

The overall incidence of ARDS was 3.85% in LTOWB and 3.60% in CT groups (95% CI, 0.84 to 2.17, p=0.21), suggesting a non-significant trend toward increased risk of ARDS with LTOWB transfusion. Dilday et al., and Hatton et al., were major contributors to this data, with Dilday et al., reporting an OR of 2.16 (CI, 0.90 to 5.17) and Hatton et al., an OR of 1.24 (CI 0.62 to 2.50), both indicating increased risk of LTOWB [35,38]. There was one outlier, Duchesne et al., reported decreased risk of ARDS following transfusion with LTOWB (OR: 0.09, 95% CI, 0.01 to 1.61), likely due to the small sample sizes or event counts [36]. There was minimal heterogeneity amongst the studies (I^2=0%, het. p=0.43), suggesting that the study outcomes are relatively consistent. This consistency provides strength in the observation that LTOWB might carry a slightly higher, albeit non-significant, risk of ARDS compared to CT. Given the pro-inflammatory nature of trauma, in conjunction with additional inflammatory processes during transfusion, the development of ARDS may be more influenced by a patient's baseline condition, rather than transfusion product.

The shared objectives of CT and LTOWB

The lack of significance between LTOWB and standard CT regarding the incidence of adverse outcomes can be attributed to the products themselves being identical, as they aim to serve the same purpose. The idea of a 1:1:1 ratio for DCR is met either through a combination of components such as in CT, or in a whole unit of LTOWB. Whole blood transfusion (either through CT and LTOWB) aims to restore blood volume, improve oxygen delivery to tissues and maintain haemostasis. Given that the physiological effects of both methods are identical, it is unsurprising that similar adverse outcomes were observed between the two groups. There are several differences between the two modalities, such as increased non-haemostatic fluids in CT and a generally higher haematocrit, platelet count and coagulation factors in LTOWB, depending on filtration methods, however these may not prove significant in influencing the incidence of PE, DVT, AKI or ARDS [12,13].

AABB titre definition

According to the Association for the Advancement of Blood and Biotherapies (AABB) standard 5.27.2, the definition of "low titre" must be defined by the institution, with product titres from the included studies ranging from <1:50 to <1:256 [10]. Three studies reported a titre level of <1:256, one study reported a level of <1:250, another reported <1:100 and one study had a titre level of <1:50 [34,36-39,41]. One study only specified that their products were "low titre" but did not provide parameters and two studies indicated varying titres due to being conducted over several institutions, however they were still considered "low titre" [35,40,42]. A review by Yazer et al., outlined the importance of standardising titre definitions in whole blood transfusion [44]. This variability in defining "low titre" reduces the validity of comparisons amongst studies, as the clarity around the safety and efficacy of LTOWB in trauma resuscitation is diminished due to significant confounders. Establishing a standardised, universally accepted definition of "low titre" should be considered to ensure a clearer understanding of transfusion product outcomes.

Leukoreduction

LTOWB leukoreduction practices are varied, with some filters sparing platelets, while others remove all white cells, or with the absence of filters entirely (i.e., 'non-leukoreduced') [45]. When compared to packed RBC, units are leukoreduced to reduce risks of febrile non-haemolytic transfusion reactions, alloimmunisation and cytomegalovirus transmission [46]. Six studies specified that their LTOWB units were leukoreduced, however the type of filtering varied from platelet-sparing to unspecified [35,37,39-42]. One study specified non-leukoreduced LTOWB, while three studies did not clarify whether their units were leukoreduced or not [34,36,38,43]. This variability in leukoreduction practices among the studies introduces a significant confounder when evaluating the safety and efficacy of LTOWB transfusion regarding adverse outcomes. A study by Haddaway et al., indicated that platelet function is moderately reduced following leukoreduction with a platelet-sparing filter [45]. Platelet function is crucial for maintaining haemostasis, with significant implications in trauma settings if platelet function is compromised, such as prolonged bleeding or coagulopathy. Depending on the leukoreduction filter used, the inability to effectively utilise platelets in LTOWB may compromise the haemostatic response during DCR. Additionally, the use of non-leukoreduced LTOWB introduces further variation as it is difficult to determine the specific influence on adverse outcome development [47].

CONCLUSION

In conclusion, LTOWB is a viable alternative to CT for trauma resuscitation, with no significant increased risk of transfusion-related complications such as PE, DVT, AKI, or ARDS. Although LTOWB may not fully mitigate the unpredictable effects of trauma, the rate of adverse outcomes is comparable to standard CT. Additionally, the use of fewer products from fewer donors offers a significant advantage in reducing the risk of adverse events. Despite the lack of statistical significance in these outcomes, the implementation of LTOWB remains a practical option, but should be considered in the context of the institution's specific needs. Ultimately, the decision between LTOWB and CT should be based on patient demographics and resource availability, to optimise patient outcomes in civilian trauma settings.

LIMITATIONS

This review is not without limitations. One significant bias to consider is confirmation bias, where institutional preferences for transfusion protocols (LTOWB *vs.* CT) may have influenced the interpretation of results, significantly reinforcing pre-existing expectations of recommending LTOWB. Selection and performance biases were prevalent across all four parameters. Particularly in smaller studies where the absence of blinding practices likely introduced selection, reporting and detection biases, significantly skewing the result. Larger studies disproportionally influenced outcomes for DVT. The analysis of AKI appeared more consistent; however, attrition bias may still be present due to inconsistencies in testing follow-up and data completeness across studies. The identified biases emphasise the need for more rigorously designed studies with larger sample sizes and standardised methods, to better assess the incidence and risks of adverse outcomes following transfusion with LTOWB or CT during initial trauma resuscitation.

FUTURE SCOPE

The outcome of this systematic review and meta-analysis did not show a clear advantage for LTOWB over CT, but also didn't diminish the value of LTOWB as a transfusion product. Using fewer products from fewer donors offers a significant advantage in reducing the risk of adverse events. LTOWB remains a viable alternative when used during the initial resuscitation of trauma patients, offering balanced composition with simplified transfusion logistics. The decision to implement LTOWB should be guided by the institution's requirements, patient demographics and operational logistics, to ensure effective use of transfusion products while minimising waste and maximising patient outcomes. While LTOWB may be more cost-effective (per unit), the literature suggests maximal benefit is seen when utilised in trauma resuscitation [14, 27-29]. Therefore, patient demographics must be carefully considered to avoid wastage, where CT may be preferable due to its versatility.

Further research is required to address limitations and biases. Prospective, randomised control trials comparing LTOWB and CT during trauma resuscitation are required to confirm LTOWB's efficacy and safety, with a focus on standardised diagnostic criteria for PE, DVT, AKI, ARDS and standardised product specifications (e.g. titre and leukoreduction). Such trials are underway to investigate these outcomes [47]. Larger sample sizes will be necessary to detect subtle yet clinically significant differences.

As time to transfusion following traumatic injury is significant in improving patient mortality rates [5,6], future studies should consider time to transfusion when observing the risk of adverse outcomes, beyond just the type of product used.

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