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Review Article

# The efficacy of Massive Transfusion Protocol /Whole Blood Transfusion: An Umbrella Review

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**Abstract**

**Introduction:** Although massive transfusion protocol (MTP) has been used extensively in the treatment of patients with bleeding trauma, its actual efficacy remains unknown. This umbrella review of systematic reviews and meta-analyses aims to update the evidence and assess the impact of implementing MTP/ whole blood transfusion on the mortality of trauma patients.

**Methods:** Data sources: This umbrella review searched Medline (via Ovid), Embase, PubMed, Cochrane Library, CINAHL databases, JBISRIR, Epistemonikos, EPPI-Centre, CRD, and PROSPERO for possible systematic reviews from inception until October 2023. Study eligibility criteria, participants, and interventions: Reviews that reported data comparing different types of massive blood perfusion were included. The quality of studies was evaluated using the Joanna Briggs Institute (JBI) critical appraisal tool. Our study outcomes, 30-day mortality, and 24-hour mortality, were re-analyzed using Comprehensive Meta-Analysis Software (CMA 3.0).

**Results:** Thirty studies met the eligibility criteria. Eventually, we included eight studies in the current meta-analysis. The calculated odds ratio (OR) and 95% confidence interval (CI) for 30-day mortality in MTP and non-MTP comparison was OR = 0.654, 95% CI: 0.576, 0.741, P-value <0.001, and similarly, when comparing the whole blood group and blood component group, significant differences were found between the groups in terms of 24h-mortality 0.763, (95% CI: 0.608, 0.957), and P-value = 0.020. The results showed low heterogeneity among the studies.

**Conclusion:** Our results support that MTP decreases 30-day mortality compared to non-MTP. Furthermore, our analysis showed that whole blood transfusion decreases the odds of 24-hour mortality compared to blood components.

**Keywords:** Massive blood transfusion, Trauma, Systematic Review

## Introduction

In both civilian and military contexts, trauma is a leading cause of global mortality, with many preventable deaths attributed to uncontrolled bleeding shortly after injury [1, 2]. Traumatic injury is a leading cause of death worldwide, accounting for approximately 10% of global deaths, particularly in the young population. Uncontrolled bleeding is the leading cause of potentially preventable death in trauma patients. Also, 80% of deaths in the operating room and half of the deaths within 24 hours after trauma are related to delayed bleeding and coagulation problems [3, 4]. Effective hemorrhage management involves early hemostasis, correction of coagulation abnormalities, maintenance of tissue perfusion, and minimizing adverse responses to shock and resuscitation fluids. Massive blood transfusion (MT) is often necessary for critically bleeding trauma patients to achieve hemostatic resuscitation. While the definition of MT varies, it is primarily defined as the transfusion of 10 or more units of packed red blood cells (RBC) in 24 hours [3, 5-8]. Of course, in the definition of MT, 3 cases are usually stated as 1- a transfusion of ≥ 10 units of RBC within 24 hours, 2- a transfusion of more than four units of RBC in 1 hour with anticipation of the need for transfusion of more blood products, and 3- replacing more than 50% of the total blood volume (TBV) with blood products within 3 hours [9]. The goal of MT is to limit the complications of critical hypoperfusion [6]. The primary indication for MT is any condition that results in acute blood loss and hemodynamic instability. The indications of MT are not limited to bleeding caused by trauma, childbirth complications, surgery, and gastrointestinal bleeding [3, 8]. Identifying the right patient who needs MT at the right time and organized management is critical to achieving optimal outcomes. Massive transfusion protocols (MTP) worldwide guide clinicians to initiate resuscitation by transfusing blood products based on specific ratios and types. The optimal ratios and types of blood products remain a topic of debate. However, most MTPs emphasize the importance of early access to blood products and hemostatic interventions for the survival of patients with severe bleeding. MTPs are designed to facilitate targeted replacement of blood components during severe hemorrhage, incorporating predefined volumes of different blood products and procoagulant agents to reduce the risks associated with excessive crystalloid administration and isolated red blood cell transfusion [10]. The critical role of blood transfusion in the management of various medical conditions, including trauma, surgery, and acute bleeding disorders, cannot be overstated. However, blood transfusion also carries risks, such as adverse reactions, complications, and the potential for blood shortages. Therefore, optimizing blood transfusion strategies is essential to maximize benefits and minimize harms. Recent advancements in blood transfusion practices, including the development of MTPs, can potentially improve patient outcomes. However, the effectiveness and safety of these protocols remain a subject of ongoing debate. Despite the widespread adoption of MTPs in trauma centers, their actual effectiveness has not been definitively established. This umbrella review of systematic reviews and meta-analyses aims to update the evidence and assess the impact of implementing MTP/ whole blood transfusion on the mortality of trauma patients.

## Methods

The current article is an umbrella review investigating the efficacy of massive blood Transfusion Protocol (MTP). Based on the initial search of published studies on this topic, extensive studies were found, so the research team decided to continue the study in the form of an umbrella review and re-analyze the systematic review and meta-analysis studies on this topic. For this purpose, a search was conducted to find relevant systematic reviews with or without meta-analysis.

In the present study, the search was done without considering language and time limitations, and all the studies were searched from the beginning to October 2023. Our search strategy is summarized in Appendix 1. Medline (via Ovid), Embase, PubMed, Cochrane Library, and CINAHL databases were searched for relevant studies. In addition to the above databases, JBISRIR, Epistemonikos, EPPI-Centre, CRD, and PROSPERO were searched for possible systematic reviews. Also, the list of sources and references of all selected articles and reports were reviewed and added to the analysis if they were eligible. After checking the English summary of the articles in languages other than English or Persian and related to the title, a translator was used to translate the articles.

Appendix 1: Search strategy

| Search | Query |
|---|---|
| #1 | ("Accidents"[Mesh]) OR "Accidents, Traffic"[Mesh] |
| #2 | (((((((((("Wounds and Injuries"[Mesh]) OR "Multiple Trauma"[Mesh]) OR "Rupture"[Mesh]) OR "Blood Loss, Surgical"[Mesh]) OR "Hemorrhage"[Mesh]) OR "Hemodynamics"[Mesh]) OR "Uterine Hemorrhage"[Mesh]) OR "Postpartum Hemorrhage"[Mesh]) OR "Aortic Aneurysm"[Mesh]) OR "Gastrointestinal Hemorrhage"[Mesh]) OR "Shock"[Mesh]) OR "Shock, Hemorrhagic"[Mesh] |
| #3 | ((((((((((("Wounds and Injuries"[Mesh]) OR "Multiple Trauma"[Mesh]) OR "Rupture"[Mesh]) OR "Blood Loss, Surgical"[Mesh]) OR "Hemorrhage"[Mesh]) OR "Hemodynamics"[Mesh]) OR "Uterine Hemorrhage"[Mesh]) OR "Postpartum Hemorrhage"[Mesh]) OR "Aortic Aneurysm"[Mesh]) OR "Gastrointestinal Hemorrhage"[Mesh]) OR "Shock"[Mesh]) OR "Shock, Hemorrhagic"[Mesh]) OR (("Accidents"[Mesh]) OR "Accidents, Traffic"[Mesh]) |
| #4 | ((((((((((((((((((((((((Multitrauma*[Title/Abstract]) OR (Trauma*[Title/Abstract])) OR (Polytrauma*[Title/Abstract])) OR (Injur*[Title/Abstract])) OR (Wound*[Title/Abstract])) OR (Rupture*[Title/Abstract])) OR (Stabwound[Title/Abstract])) OR (blood loss*[Title/Abstract])) OR (Hemorrhage*[Title/Abstract])) OR (Bleeding[Title/Abstract])) OR ("Surgical Blood Loss*"[Title/Abstract])) OR ("Surgical Hemorrhage*"[Title/Abstract])) OR (traffic[Title/Abstract])) OR (accident*[Title/Abstract])) OR (hemodynamic*[Title/Abstract])) OR ("Uterine Hemorrhage*"[Title/Abstract])) OR ("Uterine Bleeding*"[Title/Abstract])) OR ("Vaginal Bleeding*"[Title/Abstract])) OR ("postpartum bleeding*"[Title/Abstract])) OR ("Postpartum Hemorrhage*"[Title/Abstract])) OR ("Aortic aneurysm*"[Title/Abstract])) OR ("gastrointestinal bleeding*"[Title/Abstract])) OR ("Gastrointestinal Hemorrhage*"[Title/Abstract])) OR (Hematochezia*[Title/Abstract])) OR ("Hemorrhagic Shock"[Title/Abstract])) OR (Shock[Title/Abstract])) OR ("Circulatory Failure"[Title/Abstract])) OR ("Circulatory Collapse"[Title/Abstract]) |
| #5 | Search: ((((((((((((("Wounds and Injuries"[Mesh]) OR "Multiple Trauma"[Mesh]) OR "Rupture"[Mesh]) OR "Blood Loss, Surgical"[Mesh]) OR "Hemorrhage"[Mesh]) OR "Hemodynamics"[Mesh]) OR "Uterine Hemorrhage"[Mesh]) OR "Postpartum Hemorrhage"[Mesh]) OR "Aortic Aneurysm"[Mesh]) OR "Gastrointestinal Hemorrhage"[Mesh]) OR "Shock"[Mesh]) OR "Shock, Hemorrhagic"[Mesh]) OR (("Accidents"[Mesh]) OR "Accidents, Traffic"[Mesh])) OR ((((((((((((((((((((((((((Multitrauma*[Title/Abstract]) OR (Trauma*[Title/Abstract])) OR (Polytrauma*[Title/Abstract])) OR (Injur*[Title/Abstract])) OR (Wound*[Title/Abstract])) OR (Rupture*[Title/Abstract])) OR (Stabwound[Title/Abstract])) OR (blood loss*[Title/Abstract])) OR (Hemorrhage*[Title/Abstract])) OR (Bleeding[Title/Abstract])) OR ("Surgical Blood Loss*"[Title/Abstract])) OR ("Surgical Hemorrhage*"[Title/Abstract])) OR (traffic[Title/Abstract])) OR (accident*[Title/Abstract])) OR (hemodynamic*[Title/Abstract])) OR ("Uterine Hemorrhage*"[Title/Abstract])) OR ("Uterine Bleeding*"[Title/Abstract])) OR ("Vaginal Bleeding*"[Title/Abstract])) OR ("postpartum bleeding*"[Title/Abstract])) OR ("Postpartum Hemorrhage*"[Title/Abstract])) OR ("Aortic aneurysm*"[Title/Abstract])) OR ("gastrointestinal bleeding*"[Title/Abstract])) OR ("Gastrointestinal Hemorrhage*"[Title/Abstract])) OR (Hematochezia*[Title/Abstract])) OR ("Hemorrhagic Shock"[Title/Abstract])) OR (Shock[Title/Abstract])) OR ("Circulatory Failure"[Title/Abstract])) OR ("Circulatory Collapse"[Title/Abstract])) |
| #6 | "Blood Transfusion"[Mesh] OR "Blood Component Transfusion"[Mesh] |
| #7 | ((((((("Blood Transfusion*"[Title/Abstract]) OR ("Massive Transfusion*"[Title/Abstract])) OR ("Balanced transfusion ratio"[Title/Abstract])) OR ("Massive blood transfusion*"[Title/Abstract])) OR ("Massive Transfusion Protocol"[Title/Abstract])) OR ("Blood Component Transfusion*"[Title/Abstract])) OR ("Rapid administration of large amounts of blood product*"[Title/Abstract])) OR ("Rapid transfusion of large volumes of blood product*"[Title/Abstract]) |
| #8 | ("Blood Transfusion"[Mesh] OR "Blood Component Transfusion"[Mesh]) OR ((((((("Blood Transfusion*"[Title/Abstract]) OR ("Massive Transfusion*"[Title/Abstract])) OR ("Balanced transfusion ratio"[Title/Abstract])) OR ("Massive blood transfusion*"[Title/Abstract])) OR ("Massive Transfusion Protocol"[Title/Abstract])) OR ("Blood Component Transfusion*"[Title/Abstract])) OR ("Rapid administration of large amounts of blood product*"[Title/Abstract])) OR ("Rapid transfusion of large volumes of blood product*"[Title/Abstract])) |
| #9 | Search: (("Blood Transfusion"[Mesh] OR "Blood Component Transfusion"[Mesh]) OR ((((((("Blood Transfusion*"[Title/Abstract]) OR ("Massive Transfusion*"[Title/Abstract])) OR ("Balanced transfusion ratio"[Title/Abstract])) OR ("Massive blood transfusion*"[Title/Abstract])) OR ("Massive Transfusion Protocol"[Title/Abstract])) OR ("Blood Component Transfusion*"[Title/Abstract])) OR ("Rapid administration of large amounts of blood product*"[Title/Abstract])) OR ("Rapid transfusion of large volumes of blood product*"[Title/Abstract]))) AND ((((((((((((("Wounds and Injuries"[Mesh]) OR "Multiple Trauma"[Mesh]) OR "Rupture"[Mesh]) OR "Blood Loss, Surgical"[Mesh]) OR "Hemorrhage"[Mesh]) OR "Hemodynamics"[Mesh]) OR "Uterine Hemorrhage"[Mesh]) OR "Postpartum Hemorrhage"[Mesh]) OR "Aortic Aneurysm"[Mesh]) OR "Gastrointestinal Hemorrhage"[Mesh]) OR "Shock"[Mesh]) OR "Shock, Hemorrhagic"[Mesh]) OR (("Accidents"[Mesh]) OR "Accidents, Traffic"[Mesh])) OR ((((((((((((((((((((((((((Multitrauma*[Title/Abstract]) OR (Trauma*[Title/Abstract])) OR (Polytrauma*[Title/Abstract])) OR (Injur*[Title/Abstract])) OR (Wound*[Title/Abstract])) OR |

| | |
|---|---|
| | (Rupture*[Title/Abstract])) OR (Stabwound[Title/Abstract])) OR (blood loss*[Title/Abstract])) OR (Hemorrhage*[Title/Abstract])) OR (Bleeding[Title/Abstract])) OR ("Surgical Blood Loss*"[Title/Abstract])) OR ("Surgical Hemorrhage*"[Title/Abstract])) OR (traffic[Title/Abstract])) OR (accident*[Title/Abstract])) OR (hemodynamic*[Title/Abstract])) OR ("Uterine Hemorrhage*"[Title/Abstract])) OR ("Uterine Bleeding*"[Title/Abstract])) OR ("Vaginal Bleeding*"[Title/Abstract])) OR ("postpartum bleeding*"[Title/Abstract])) OR ("Postpartum Hemorrhage*"[Title/Abstract])) OR ("Aortic aneurysm*"[Title/Abstract])) OR ("gastrointestinal bleeding*"[Title/Abstract])) OR ("Gastrointestinal Hemorrhage*"[Title/Abstract])) OR (Hematochezia*[Title/Abstract])) OR ("Hemorrhagic Shock"[Title/Abstract])) OR (Shock[Title/Abstract])) OR ("Circulatory Failure"[Title/Abstract])) OR ("Circulatory Collapse"[Title/Abstract]))) |
| #10 | ("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh]) OR ( "Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] ) |
| #11 | (("Systematic Review*"[Title/Abstract]) OR ("Meta-Analysis"[Title/Abstract])) OR ("Meta-Analyses"[Title/Abstract]) |
| #12 | (("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh]) OR ( "Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] )) OR ((("Systematic Review*"[Title/Abstract]) OR ("Meta-Analysis"[Title/Abstract])) OR ("Meta-Analyses"[Title/Abstract])) |
| #13 | Search: ((("Blood Transfusion"[Mesh] OR "Blood Component Transfusion"[Mesh]) OR (((((((("Blood Transfusion*"[Title/Abstract]) OR ("Massive Transfusion*"[Title/Abstract])) OR ("Balanced transfusion ratio"[Title/Abstract])) OR ("Massive blood transfusion*"[Title/Abstract])) OR ("Massive Transfusion Protocol"[Title/Abstract])) OR ("Blood Component Transfusion*"[Title/Abstract])) OR ("Rapid administration of large amounts of blood product*"[Title/Abstract])) OR ("Rapid transfusion of large volumes of blood product*"[Title/Abstract]))) AND (((((((((((((("Wounds and Injuries"[Mesh]) OR "Multiple Trauma"[Mesh]) OR "Rupture"[Mesh]) OR "Blood Loss, Surgical"[Mesh]) OR "Hemorrhage"[Mesh]) OR "Hemodynamics"[Mesh]) OR "Uterine Hemorrhage"[Mesh]) OR "Postpartum Hemorrhage"[Mesh]) OR "Aortic Aneurysm"[Mesh]) OR "Gastrointestinal Hemorrhage"[Mesh]) OR "Shock"[Mesh]) OR "Shock, Hemorrhagic"[Mesh]) OR (("Accidents"[Mesh]) OR "Accidents, Traffic"[Mesh])) OR ((((((((((((((((((((((((((Multitrauma*[Title/Abstract]) OR (Trauma*[Title/Abstract])) OR (Polytrauma*[Title/Abstract])) OR (Injur*[Title/Abstract])) OR (Wound*[Title/Abstract])) OR (Rupture*[Title/Abstract])) OR (Stabwound[Title/Abstract])) OR (blood loss*[Title/Abstract])) OR (Hemorrhage*[Title/Abstract])) OR (Bleeding[Title/Abstract])) OR ("Surgical Blood Loss*"[Title/Abstract])) OR ("Surgical Hemorrhage*"[Title/Abstract])) OR (traffic[Title/Abstract])) OR (accident*[Title/Abstract])) OR (hemodynamic*[Title/Abstract])) OR ("Uterine Hemorrhage*"[Title/Abstract])) OR ("Uterine Bleeding*"[Title/Abstract])) OR ("Vaginal Bleeding*"[Title/Abstract])) OR ("postpartum bleeding*"[Title/Abstract])) OR ("Postpartum Hemorrhage*"[Title/Abstract])) OR ("Aortic aneurysm*"[Title/Abstract])) OR ("gastrointestinal bleeding*"[Title/Abstract])) OR ("Gastrointestinal Hemorrhage*"[Title/Abstract])) OR (Hematochezia*[Title/Abstract])) OR ("Hemorrhagic Shock"[Title/Abstract])) OR (Shock[Title/Abstract])) OR ("Circulatory Failure"[Title/Abstract])) OR ("Circulatory Collapse"[Title/Abstract])))) AND ((("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh]) OR ( "Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] )) OR ((("Systematic Review*"[Title/Abstract]) OR ("Meta-Analysis"[Title/Abstract])) OR ("Meta-Analyses"[Title/Abstract]))) |

## Data Extraction Process

After the final selection of the studies, the required information was extracted and summarized using the designed table (Extraction table) in the Excel software environment. Endnote X10 resource management software was also used to organize study titles and abstracts and identify duplicates. The JBI Data Extraction Form for Review for Systematic Reviews and Research Syntheses was used to extract data. Data extraction was done by two reviewers separately and controlled and confirmed by a third person.

Pilot Testing: Two independent reviewers pilot-tested the data extraction form on a subset of included studies to assess clarity, completeness, and usability. The feedback from this pilot was used to refine the form.

- Independent Extraction: Two independent reviewers extracted data from each included study using the finalized extraction form. This dual-review process aimed to minimize bias and ensure accuracy in data collection.

- Duplicate Review: Each reviewer extracted data independently, and discrepancies between their extractions were resolved through discussion. If consensus cannot be reached, a third reviewer is consulted to make a final determination.

## Data Items to be Extracted

The extraction list included the author's name, publication year, purpose, participant characteristics, number of studies/participants, sources/domain searched, types of studies, critical appraisal tools and scoring, variance ratio estimate correctly reflecting the difference in effect size (I2) for publication bias, analysis method, results, and conclusions.

## Confirmation of Data from Investigators

To enhance the reliability of the extracted data, we implemented the following processes for obtaining and confirming data from study investigators:
- Contacting Authors: Where necessary, we contacted the corresponding authors of included studies to clarify any ambiguities in reported data or to obtain additional information that may not be fully detailed in the published reports.
- Follow-Up Procedures: A follow-up email is sent if the initial contact responds after two weeks.

Eligibility criteria and data extraction

In the present study, only systematic review studies with or without meta-analysis were eligible to be included.

## Exclusion criteria

Irrelevant and repetitive studies, lack of access to the full text of articles, animal studies, traditional review articles, weak connection with the purpose of the study, lack of appropriate implementation method, lack of necessary quality in terms of reporting the desired findings, books, dissertations, the letter to the editor, the editor's article, the conference article, were put aside.

Quality Assessment of the Included Studies

JBI critical evaluation tools for systematic review studies and meta-analysis were used to evaluate the quality of study methodology and the quality of evidence. The quality of clinical trial studies included in the meta-analyses was not evaluated, and only the estimated summary of each meta-analysis was used. Evaluations with less than 5 'yes' responses were excluded. In order to perform a critical appraisal of articles, two reviewers evaluated the quality of evidence independently. In case of disagreement, the issue was examined through discussion, and if the difference remained, a third evaluator was used to determine the quality of the evidence.

Definition of PICO Study:

P = patients requiring massive blood transfusion

Types of Trauma: Blunt trauma, penetrating trauma, and multitrauma.

Non-Trauma Populations: Surgical patients, medical patients, and obstetric patients.

I = massive blood transfusion.

C = other blood transfusion protocols (whole blood transfusion, red blood cell (RBC) transfusion, platelet (PLT) transfusion, and fresh frozen plasma (FFP) transfusion)

O = The primary outcome included the mortality (30-day, in-hospital, 24-hour), morbidity rate (ARDS, AKI, MOF, sepsis, pneumonia, thrombotic events, allergic reactions, acute lung injury, transfusion-associated circulatory overload) and the frequency of the secondary outcome and the use of various blood products and side effects of massive blood transfusion.Data synthesis

The majority of articles reported measures of the correlation between 30-day mortality, 24h-mortality, and massive transfusion by odds ratio (OR) and risk ratio (RR) with their corresponding confidence intervals (CI). Analyses were performed using Comprehensive Meta-Analysis Software (CMA 3.0).

The analysis used combined effects reported from systematic reviews. As a result, some primary studies may have been included in different reviews and meta-analyses in different years, and we could not exclude them. To evaluate heterogeneity among primary studies, we used forest plots, Cochran's Q statistic, and I2 statistic. When heterogeneity was high ($I2 > 50\%$), we used a random effects model with restricted maximum likelihood. If not, we applied a fixed-effects model.

# Results

## Screening and Selection Process

1. Initial Retrieval: A total of 5633 articles were retrieved from various databases.
2. Duplicate Exclusion: We identified and excluded 2697 duplicate publications during the initial screening phase.
3. Title and Abstract Screening: Following the removal of duplicates, we examined the titles and abstracts of the remaining 2936 articles. From this examination, 1362 irrelevant publications were excluded based on their titles and abstracts.
4. Full-Text Review: The full texts of 157 articles were then assessed for eligibility. After this thorough review, we excluded an additional 108 publications for various reasons, including:
   - Lack of relevant outcomes related to blood transfusion.
   - Studies focusing on populations that did not meet our inclusion criteria (e.g., non-trauma patients).
   - Insufficient data for meta-analysis.

5. Final Inclusion: Our umbrella review included 30 eligible systematic reviews. Eight studies were selected for inclusion in the meta-analysis based on their relevance and quality.

Summary of Exclusions

- Duplicated Publications: 2697
- Irrelevant Publications (Title/Abstract Screening): 1362
- Excluded After Full-Text Review: 108
  - Reasons include lack of relevant outcomes, inappropriate population focus, and insufficient data.

## Data Extraction

We extracted key characteristics and outcomes from the included studies, as detailed in Tables 1 and 2. Figure 1 presents the PRISMA flow chart illustrating this selection process, providing a visual representation of the screening stages.

## Characteristics of included studies

The systematic reviews were conducted in 12 countries. The included articles were published between 2002 and 2023. The number of participants was between 234 and 35386. Articles were from 14 different countries from the USA (seven), England (seven), Canada (six), Australia (three), Netherlands (three), Denmark (two), Japan (one), Qatar (one), Israel (one), Colombia (one), Switzerland (one), Italy (one), Austria (one), Korea (one), and Austria (one). Included articles have consisted of military trauma patients, civilian trauma patients, and non-trauma patients in our review.

Fifteen studies reported the clinical outcomes of FFP: RBC and Plt: RBC, and four reported the clinical outcomes of whole blood transfusion. The mean age of the included articles was varied. Two articles included the pediatric population [11, 12], and one article obstetrics population [11]. Ten studies concluded that a high ratio of FFP: RBC and Plt: RBC reduced mortality and had better survival outcomes. Four studies reported the effect of whole blood transfusion on mortality. All four studies reported that mortality in the intervention and control groups is equivalent. Three studies evaluated prehospital blood transfusion in patients, and all three articles concluded no differences between the groups in terms of mortality. Several side effects were reported after the transfusion, including ARDS, AKI, MOF, sepsis, pneumonia, thrombotic events, allergic reactions, acute lung injury, and transfusion-associated circulatory overload. Additional information about included studies is summarized in Table 1 and Table 2. Curry et al. reported that Plt transfusion is not associated with lower mortality in trauma patients [13]. Also, Rajasekhar et al. stated that FFP: PRBC 1:1 was not associated with lower mortality, and more randomized clinical trials are warranted [1]. Carson et al., in a systematic review and meta-analysis of surgical and trauma patients, reported that conservative blood transfusion did not lower the mortality and cardiac event outcome (OR, 0.80[95%CI: 0.63,1.0), and OR 0.76, 95%CI: 0.67,1.00]).

## Characteristics of included studies for meta-analysis

From eight included studies for meta-analysis, five studies compared the MTP and non-MTP for 30 days and in-hospital mortality [8, 14-17], and three studies compared the whole blood and blood component transfusion for 24h mortality [18-20]. Table 3 summarizes the information about mortality OR. The number of studies in each meta-analysis ranged from 4 to 27. Study patients were with blunt or penetrating trauma and non-trauma, and it included civilian and military trauma. Two studies reported that 30-day mortality was significantly lower in the MTP group [8, 17]. In comparison, six studies showed no differences between the MTP and non-MTP groups regarding 30-day mortality MTP or whole blood transfusion groups [8, 15, 16, 18-20]. Consunji et al. showed lower RR in overall mortality (OR 0.69 [0.55-0.86]) [8]. Three studies compared the association of whole blood transfusion between 24-hour mortality and 30-day mortality [18-20]. Von der Host et al. reported that 24h mortality was lower in the civilian population (OR, 0.71; 95% CI, 0.52–0.98) [18]; however, one study reported that 24h mortality did not differ between the whole blood group and blood component (OR 0.80, 95% CIs 0.40, 1.59), and Crowe et al. revealed that whole blood is not associated with 30-day mortality and 24h-mortality (OR, 0.79; 95% CI, (0.48–1.31, and OR 0.83; 95% CI, 0.56–1.24) [19, 20].

Figure 2 shows the pooled OR of included studies for 30-day and in-hospital mortality using the fixed effect (OR = 0.654, 95% CI 0.576, 0.741, P-value = 0.000). The MTP group had lower odds of 30-day mortality compared to the non-MTP group. Figure 3 is a forest plot for 24h mortality. The pooled OR (95% CI) using the fixed effect from three studies is 0.763, (0.608, 0.957), and P-value = 0.020. Similar to the 30-day mortality, massive transfusion reduced the odds of mortality. Results were not associated with significant statistical heterogenicity among the studies (I2 = 0%, P-value<0.001). Additional analysis information is summarized in Table 4.

## Methodological quality assessment

The quality of studies was evaluated using JBI criteria (Table 5). According to the results of JBI quality assessment checklists for systematic review and meta-analysis, most of the studies were of moderate to high quality.

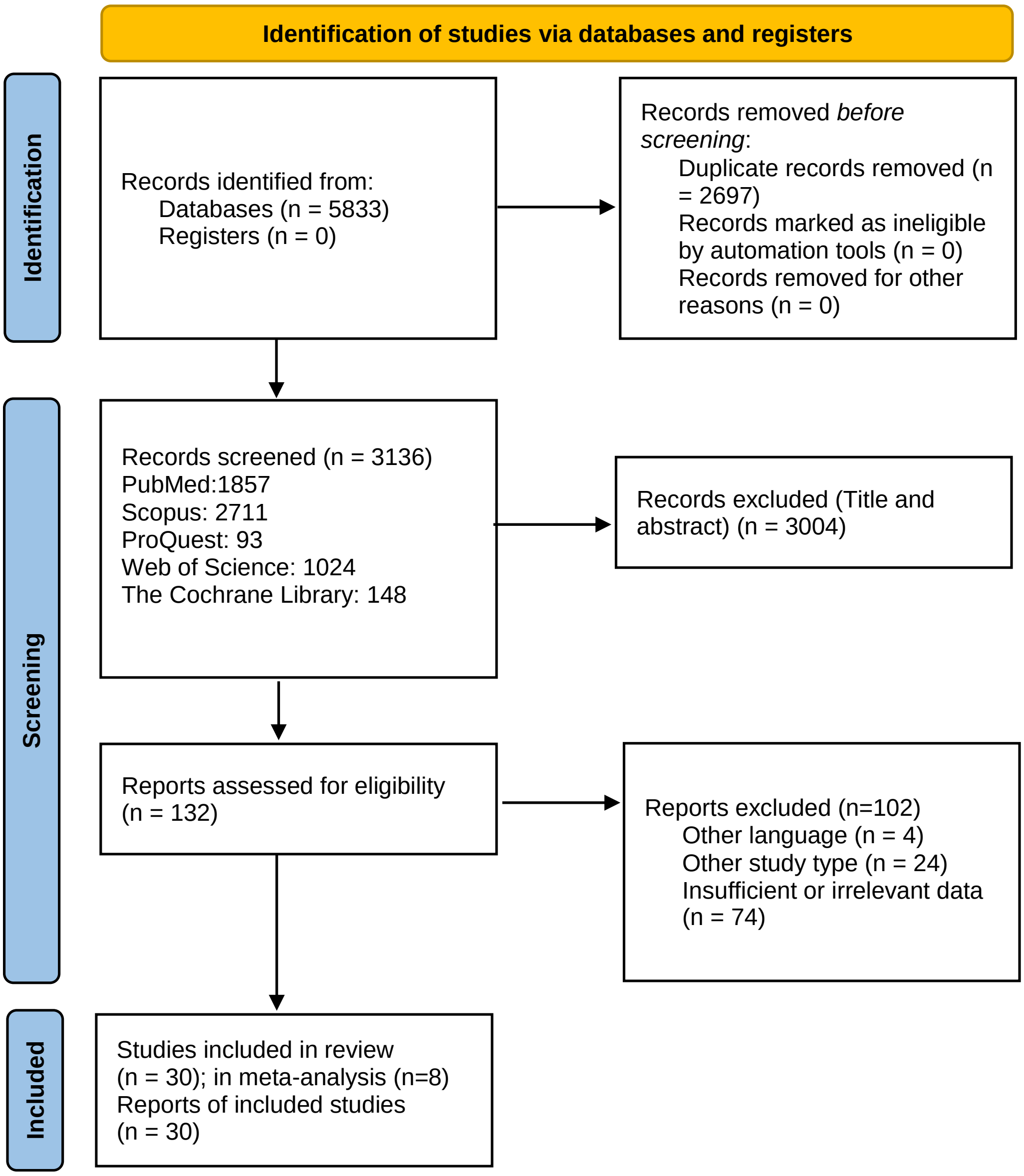


Figure 1: Flowchart of the included eligible studies

Table 1: Characteristics of the included studies

| Study | Year | Country | Type of Study | Type of trauma | Cause of injury | Participants | Adverse effect |
|---|---|---|---|---|---|---|---|
| van der Horst [18] | 2023 | Netherland | Systematic review and meta-analysis | Civilian and military trauma | trauma | - | ARDS, AKI, pneumonia, pulmonary embolism |
| Bhangu [25] | 2012 | England | Systematic review and meta-analysis | Civilian and military trauma, blunt trauma | blunt trauma | 1885 | |
| Johansson [14] | 2012 | Denmark | Systematic review and meta-analysis | - | closed head injury, traumatic injury | 3663 | - |
| Patel [26] | 2014 | Canada | Systematic review and meta-analysis | polytrauma-major torso trauma-blunt trauma | head-hepatic-splenic injury | 1262 | MOF, ARDS |
| Kang [27] | 2019 | Korea | Systematic review and meta-analysis | - | acute lung injury | 17511 | - |
| Carson [28] | 2002 | USA | systematic review and meta-analysis | Surgical and trauma patients | acute severe upper GIH-acute hemorrhage- cardiac surgery-critical care-vascular surgery-orthopedic surgery | 1780 | - |
| Murad [29] | 2010 | USA | systematic review and meta-analysis | blunt and penetrating trauma | trauma and surgery | 12421 | - |
| Stanworth [30] | 2004 | England | systematic review of randomized clinical trials | - | - | 234 | - |
| Phan [31] | 2009 | USA | systematic review | combat trauma-penetrating trauma-blunt trauma- head trauma- consecutive trauma | trauma and penetration | 3430 | Acute respiratory distress syndrome (ARDS) |
| Curry [13] | 2011 | England | systematic review of clinical trials | blunt and penetrating trauma | acute lung injury abdominal injury and kidney injury | 1374 | multi-organ failure (MOF), ARDS, and infection |
| Langenecker [32] | 2011 | Austria | a systematic review (RCT, prospective, retrospective, and non-RCT) | massive trauma | Surgery (ischemic colitis)- CV surgery-Various - surgery (TIC)- Surgery (craniofacial, infants)- Surgery (various) with massive transfusion-Surgery (hepatectomy for hepatocellular carcinoma)- Liver transplantation - CV surgery (pediatric) | 35388 | thrombotic events, acute lung injury (ALI), transfusion-associated circulatory overload (TACO), infections (bacterial contamination and viral transmission), and MOF |
| Rajasekhar [1] | 2011 | Canada | systematic review | military trauma-blunt trauma-penetrating trauma | traumatic injury | 3107 | ARDS and MOF increased with a higher FFP: PRBC ratio |
| Vogt [17] | 2012 | Canada | systematic review and meta-analysis | blunt trauma and civilian trauma | - | 1801 | - |
| Hallet [33] | 2013 | Canada | systematic review | 1. Civilian, massive bleeding, blunt 2. Civilian, nonpassive, penetrating 3. Military, massive bleeding, | - | 4230 | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | penetrating<br>4. Civilian, massive bleeding, blunt<br>5. Civilian, massive bleeding, penetrating | | | |
| Mitra [15] | 2013 | Australia | systematic review and meta-analysis | Trauma patients | - | 1868 | |
| McQuilten [34] | 2015 | Australia | systematic review | hemorrhaging trauma, blunt trauma, penetrating trauma, massive transfusion trauma, torso and/or proximal lower extremity bleeding | upper gastrointestinal hemorrhage | - | ARDS |
| Smith [35] | 2016 | England | systematic review | penetrating trauma, blunt trauma, blast, non-trauma | RTA, RTC, Explosive, motor vehicle accident, gunshot wound | - | Infection and MOF |
| Tanaka [11] | 2017 | Japan | systematic review | - | traumatic bleeding-obstetric-related bleeding - postpartum bleeding - disseminated intravascular coagulation (DIC) | - | - |
| Teodoro da Luz [22] | 2019 | Canada | systematic review and meta-analysis | bleeding trauma | - | 27977 | - |
| Kamyszek [36] | 2018 | USA | systematic review | blunt and penetrating trauma | - | 18369 | - |
| Rijnhout [37] | 2019 | Netherland | systematic review and meta-analysis | civilian trauma | blunt and penetrating trauma, motor vehicle accident, gunshot wound, explosive | 5159 | allergic reaction, breathing depression, anaphylaxis, hypotension and urticaria. |
| Shand [38] | 2018 | Australia | systematic review | hemorrhaging trauma, civilian and military trauma | blunt and penetrating trauma - hemorrhagic trauma | - | - |
| Sommer [16] | 2018 | Switzerland | systematic review and meta-analysis | Trauma and non-trauma patients | - | 2475 | pulmonary disease, bleeding diathesis, cardiovascular |
| Avery [39] | 2019 | England | systematic review | - | blunt and penetrating trauma, polytrauma | 3255 | ARDS, Acute Kidney Injury (AKI), Multiple Organ Dysfunction Syndrome (MODS), embolic events, and transfusion reactions. |
| Consunji [8] | 2020 | Qatar | systematic review and meta-analysis | bleeding trauma, civilian trauma, military trauma | abdominal aortic injury, grade 4 liver injury | 3201 | - |
| Crowe [19] | 2020 | USA | systematic review and meta-analysis | military trauma, combat related thoracic trauma, civilian trauma, blunt trauma , | traumatic hemorrhagic shock, | 8430 | - |
| Kinslow [12] | - | USA | systematic review | pediatric trauma, blunt trauma | blunt and penetrating trauma, burn | 2345 | High ratio of FFP:RBC 2:1 is correlated with DVT and high |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | ratio of Plt:RBC 2:1 is corelated with pneumonia |
| Ritchie [40] | 2020 | England | systematic review of RCT | - | - | 1106 | thromboembolic events, MOF, and sepsis |
| Rodrígueza [41] | 2020 | Colombia | systematic review and meta-analysis | civilian trauma, | - | 13945 | - |
| Cruciani [20] | 2020 | Italy | systematic review and meta-analysis | military trauma, civilian trauma, traumatic brain injury | traumatic brain injury, traumatic injury , chest injury | 3642 | - |
| Malkin [42] | 2020 | Israel | systematic review | Hemorrhaging Trauma, combat trauma, civilian trauma , military trauma, | traumatic brain injuries, blunt and penetrating injury | 1292 | higher rate of ARDS in whole blood group and AKI |
| Jones [43] | 2016 | USA | Systematic review | millitary trauma, civilian trauma | blunt and penetrating trauma | 424 ± 280 range of 21– 1,250 | MOF, nosocomial infections, ARDS, ARF Sepsis |

Table 2: Outcome reported of the included studies

| study | Approach | Intervention details | Need to hospital admission | Time of hospitalization | Outcome |
|---|---|---|---|---|---|
| van der Horst [18] | Whole blood vs. blood component | - | Yes | - | Whole blood had lower mortality in the 24h-mortality endpoint (0.71; 95% CI, 0.52–0.98). |
| Bhangu [25] | High ratio vs low ratio FFP: RBC | - | yes | - | Ratios higher than 1:2 were associated with lower mortality risk in comparison with lower ratios. |
| Johansson [14] | High ratio vs low ratio FFP: RBC / Plt: RBC | FFP: RBC ratio high vs low AND PLT: RBC ratio high vs low | yes | - | The high ratio of FFP:RBC and Plt:RBC is correlated with significantly lower mortality risk OR: 0.49; 95% ( 0.43-0.57); P<0.0001 |
| Patel [26] | Odds of Mortality and Adverse Effects of RBC transfusion | - | yes | - | One unit increase in RBC transfusion is correlated with a higher risk of mortality OR 1.07, 95%CI 1.04–1.10, P < 0.001) |
| Kang [27] | Specificity and sensitivity of MT FFP: PRBC | resuscitation intensity (RI), defined as the sum of each unit of resuscitation product, including each unit of blood product (PRBC, plasma, or platelets), every 500 mL of colloid solution, and every 1,000 mL of crystalloid solution administrated within the first 30 minutes | yes | - | MT demonstrated high specificity as a predictor for overall mortality |
| Carson [28] | Conservative blood transfusion | - | yes | | Conservative blood transfusion does not affect mortality and cardiac events 0.80 [0.63,1.0) 0.7610.67,1.00]. |
| Murad [29] | High ratio vs low ratio FFP: RBC / Plt: RBC | plasma 2U to 8U daily for 3 days/ plasma 300 mL/6 hr until PT ratio normalizes/ plasma 12 mL/kg and RBC 11mL/kg | yes | - | Plasma transfusion decreases mortality and MOF rate, patients who received MTP undergoing surgery had lower mortality, and plasma transfusion was correlated with a high risk of ALI OR, 0.38; 95% [CI, 0.24-0.60], (OR, 1.22; |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | 95% CI, 0.73-2.03), OR, 2.92; 95% CI, 1.99-4.29 |
| Stanworth [30] | FFP | FFP 300 ml/ 6 h (600 ml if prothrombin time ratio >7) in liver disease - FFP 2 units adults and 1 unit child in cardiac surgery with bypass - FFP 10 ml/kg/d for 7 days in HUS - FFP 10 ml/kg for 2 days in prevention IVH - FFP 15 ml/kg in neonatal sepsis - FFP 10 ml/kg for 3 days in preterm - FFP 200 ml/m2/days in burns of adults and children - Partial plasma exchange with FFP in Neonates polycythemia - FFP 7 ml/kg in lung disease | yes | - | No differences in mortality |
| Phan [31] | High ratio of plasma platelets to RBC | FFP:pRBC (<1:1.5 ration / < 1:2 ratio / < 2:3 ratio / <=1:8 ratio / <1:4 ratio ) | yes | - | Increased ratio of plasma and platelets decrease the mortality rate |
| Curry [13] | FFP and blood substitute | 6U plts with every 12U whole blood (contains ~ 420ml plasma),2U FFP with every 12U whole blood (~440ml plasma) and Allogeneic transfusions | yes | - | Platelet transfusion is not associated with lower mortality rate |
| Langenecker [32] | FFP:RBC vs. Fibrinogen | Colloid, crystalloid or no intervention - Alternative dosage or formulation - Fibrinogen concentrate vs FFP (FFP 2U to 14U OR 10-45 mL/kg) | yes | ICU stay > 10 days | FFP alone, did not appeared to be effective in clinical outcomes. Besides higher ratio of FFP:RBC was correlated with lower mortality. |
| Rajasekhar [1] | high vs. low FFP/PRBC | FFP:PRBC (<1:1 to 1:2, 1:3, 1:4, 1:5, 1:8) | yes | 20.7+-18 days to 49.3+-53.4 days | Evidences did not support the idea of FFP:PRBC 1:1 ratio is correlated with better survival outcome |
| Vogt [17] | MTP | Blood products delivered through the use of a formal TTP: 1. Initial response: 10 U PRBC + 4 U thawed plasma + 2 U single donor platelets If continued:6UPRBC+4Uplasma+2Usingle donor platelets/ 2. Initiation package: 6 U PRBC + 6 U thawed plasma Additional packages (q30 min): 6 U PRBC + 6 U plasma + 1 apheresis U platelets in every other pack + 20 U cryoprecipitate in package 2, and 10 U every other pack after + rFVIIa 3·6 mg dose in package 3, repeat dose 30 min later if required/ 3. Transfusion packages containing 5 U PRBC + 5 U thawed plasma + 2 U platelet concentrate Monitored by thromboelastographic in ER/OR/ 4. Initiated by trauma team Shipments: 5 U PRBC + 2 U thawed plasma + 1 platelet dose (6 pooled or 1 apheresis unit) in every other shipment + rFVIIa 4·8 mg dose in shipment 3 + rFVIIa 2·4 mg dose in shipment 6/ 5. Activated by attending physician (recommended if > 4 U PRBC in 4 hours or expected transfusion requirements > 10 U PRBC in 12 hours) - Packs: 6 U PRBC + 4 U thawed plasma + 1 U apharesis platelets/ 6. Activated by attending physician after transfusion of 4 U PRBC- Trauma packs: 4 U PRBC + 4 U plasma + 1 set of platelets in every other pack + Consider rFVIIa (weight-based dose) with pack 3, repeat in pack | yes | - | Formal trauma transfusion pathway is related with lower rate of mortality in trauma patients |

| | | | | | |
|---|---|---|---|---|---|
| | | 4 if required + Cryoprecipitate available upon request at any time | | | |
| Hallet [33] | Higher Platelet:RBC Ratio | 1. Civilian, massive bleeding, blunt (Low, > 1:20 Mid, 1:2 High, 1:1 with type of platelet: 1 Apheresis converted to 6 pooled units) / 2. Civilian, nonmassive, penetrating (Low, < 1:1 High, ≥ 1:1) / 3. Military, massive bleeding, penetrating (Low, < 1:16 Mid, 1:16–1:8 High, ≥ 1:8 with type of platelet: Apheresis) / 4. Civilian, massive bleeding, penetrating (Low, < 1:18 Mid, 1:18–1:12 High, 1:12–1:6 Highest, ≥ 1:6 with type of platelet: 1 apheresis = 3 or more pooled units / 5. Civilian, massive bleeding, blunt (Pre-TP, 1:0.6 MTP, 1:1.2 with type of platelet: Single-donor units) | yes | - | Higher Platelet:RBC Ratio is associated with lower mortality rate in massive blood loss |
| Mitra [15] | MTP | ratio of FFP: PRBC significant increase in the proportion of injured patients receiving a high transfusion ratio (pre-MTP 55% to MTP 85%; P < 0.001)./ Significant change in the ratio of platelet : PRBC (pre-MTP 1:1.7 versus MTP 1:1.3, P < 0.05). Reported significantly higher volumes of platelet administration with an MTP and significantly higher platelet PRBC ratios/ No significant change in cryoprecipitate administration volumes or ratios of cryo : PRBC associated with the introduction of their MTP. / MTP that mandated rFVIIa was a significant increase in administration (pre-MTP 0.63 mg/patient versus MTP 1.91 mg/patient, P < 0.002). / significant reduction in intra-operative fluid volume administration (pre-MTP 7.0 L versus MTP 4.8 L, P < 0.001) and a mean reduction of 5 L of crytalloid per patient (pre-MTP 14.0 L versus MTP 9 L), respectively. ((((3.6 to 4.8 mg rFVIIa after 15-18 units of PRBCs ---10 to 20 units Cryoprecipitate after 12 to 15 units of PRBCs)))) | yes | - | The calculated OR for mortality was 0.73 and MTP may not reduce mortality rate. |
| McQuilten [34] | MTP | Intervention - fixed ratio of RBCs, FFP, and PLT at 1:1:1 ratio /Intervention—6 WB units and Control—6 RBC units + 6 FFP units then Each group received 1 PLT / Three intravenous doses of rFVIIa (200 g/kg at 0 h, 100 g/kg at 1 h and 3 h) orplacebo / rFVIIa 3 doses (200 µg/100 µg/100 µg) given after 8th RBC unit, then 1 and 3 h vs placebo ----- Co-interventions (ventilator, angioembolization, craniectomy Crystalloid, Colloid, Cryoprecipitate, rFVIIa, Tranexamic acid Endoscopic guidelines, recommendations for PPIs, somatostatin, antibiotics) | yes | 9.6 to 11.5 days | More studies is required to evaluate the high FFP:RBC ratio and MTP in patients requiring massive blood transfusion. |
| Smith [35] | Prehospital blood products | In military studies, PHBP recipients were managed more aggressively, receiving 2.5 times more PTC crystalloid, more in hospital PRBC, and more platelet transfusions | yes | - | No difference in clinical outcome and mortality. |

| | | | | | |
|---|---|---|---|---|---|
| Tanaka [11] | MTP in obestricts | FFP/RBC ratio exceeds 1 at 12 h following the onset of obstetric haemorrhage./ Medically necessary FFP/RCC ratio is 1.3 in obstetric hemorrhage. / MTP was defined as a combination of 6 units of O-negative RBC, 4 units of FFP (liquid AB plasma or thawed type specific plasma), and 1 apheresis platelet (PLT) unit. / FFP/RBC ratio >= 1 required during massive obstetrics hemorrhage. /Transfusion of FFP/RBC ratio >= 1 reduces mortality during amniotic fluid embolism with coagulopathy / the calculated FFP/RBC ratio was 1.3 when converted from whole blood / The "Green-top Guideline: Blood Transfusion in Obstetrics" recommends 12e15 ml/kg of FFP for every 6 units of RBC and This guideline further recommends administration of cryoprecipitate as two 5-unit sets, while maintaining fibrinogen at a level of 150 mg/dl. | yes | - | FFP/RBC ratio more than 1 is associated with better clinical outcomes and could decrease the mortality |
| Teodoro da Luz [22] | High vs low FFP: RBC ratio | high ratio ( 1:1:1) and low ratio (1:1:2)/ 1:1:1 ratio group received more FFP (median of 7 units vs. 5 units) and PLTs (12 units vs. 6 units). However, patients received similar amount of RBCs (9 units) within the first 24 hours in both arms/ | yes | - | High ratio FFP: RBC showed no significant improvement in survival. Mortality was equivalent between the low ratio and high ratio groups. |
| Kamyszek [36] | Pediatrics MTP | - | yes | total LOS: 45.8 days and ICU LOS: 6 days | High mortality was reported in pediatrics requiring MTP. |
| Rijnhout [37] | prehospital blood-component transfusion | RBC+PLT /RBC + FP / RBC + cryo / RBC+PLT / RBC+FP / RBC + cryo / RBC+PLT / RBC+FP / RBC+PLT+FP / RBC+PLT+FP+cryo / PLT+cryo / FP + cryo | yes | - | prehospital blood-component transfusion is safe, but no differences were seen in long term mortality. |
| Shand [38] | Prehospital blood transfusion | Prehospital intervention: pRBCs 750 ml (250-5000) Crystalloids 1500 mL (0- 9250) / 1 to 4 units plasma / saline 150 to 900 cc | yes | - | Prehospital blood transfusion is safe, more evidence-based research is needed. |
| Sommer [16] | MTP vs non-MTP | - | yes | - | MTP did not decrease the 24h mortality and 30 day mortality |
| Avery [39] | Whole blood vs blood component | mWB (leucoreduced) + aPLT for every 6 units, FWB (nonleucoreduced) + RBC + FFP + cryo | yes | - | Conflicting report about whole blood transfusion |
| Consunji [8] | MTP vs. non-MTP | RBC + plasma + aPLT for every 6 units OR aPLT + RBC + FFP + cryo OR aPLT + RBC + plasma OR | yes | - | Overall mortality was reduced in post MTP group |
| Crowe [19] | Whole blood vs blood component | pRBC:FFP: PLP >>>>>> 6:4:4 or 1:1:1 or 6:6:8 or 5:5:4 | yes | - | Whole blood did not reduce the 24 h mortality and 30-day mortality |
| Kinslow [12] | High vs low FFP: RBC ratio And MTP in pediatrics | "low" <1:2, "medium" 1:2-1:1, "high" >1:1 FFP:RBC; also "low" 1:6, "medium" 1:6 - 1:3, "high" >1:3 plt:RBC | yes | - | Pediatric massive transfusion may reduce the mortality, but further studies are required |

| | | | | | |
|---|---|---|---|---|---|
| Ritchie [40] | Control group received 1:1 (RBC:plasma) And intervention group ratio was varied (some studies used whole blood transfusion) | mWB vs. COMP Blood Products / "low" <1:2, "medium" 1:2-1:1, "high" >1:1 FFP: RBC; also "low" 1:6, "medium" 1:6 - 1:3, "high" >1:3 plt:RBC | yes | 0- 15 days | The pooled RR fore 24h mortality and 30 day mortality was not statically significant in comparator groups (control group used 1:1). |
| Rodrígueza [41] | High vs low FFP:RBC ratio | High ratio FFP:RBC: 1:1.5, 1:2 , 1:3 , 1:4 | yes | - | The pooled OR from observational studies showed decrease in mortality in civil trauma patients. |
| Cruciani [20] | Whole blood and blood component | WB vs. COMP transfusion AND FWB vs. COMP AND FWB vs. aPLT | yes | - | Both groups were eqiuvalant in terms of mortality |
| Malkin [42] | fresh whole blood vs. cold-stored low titer type O whole blood | resuscitation volumes of crystalloid between intervention groups in the first 24 hours, which was in the 3.5 to 4-L range. / higher ratios of both plasma and PLT in the WB group (0.99 vs 0.77 and 0.72 vs .51 | yes | - | Whole blood did not improve the survival |
| Jones [43] | component transfusion in a 1:1:1 ratio | - | Yes | - | High transfusion ratio is associated with lower mortality. |

Table 3: OR and RR reported in meta-analysis

| author | approach | type of report RR or OR | mortality (30-day mortality and in hospital mortality) | | | 24-h mortality | | |
|---|---|---|---|---|---|---|---|---|
| | | | RR or OR | Q1 | Q3 | RR or OR | Q1 | Q3 |
| Vogt [17] | MTP using formal trauma transfusion pathway (TTP) | RR | 0.69 | 0.55 | 0.87 | | | |
| Mitra [15] | MTP and non-MTP | OR | 0.73 | 0.48 | 1.11 | | | |
| Sommer [16] | MTP and non-MTP groups | OR | 0.56 | 0.3 | 1.07 | *0.42* | 0.01 | 16.62 |
| Consunji [8] | MTP comparing post MTP and pre MTP | OR | 0.73 | 0.46 | 1.16 | 0.81 | 0.57 | 1.14 |
| Johansson [14] | MTP and non-MTP groups | OR | 0.62 | 0.52 | 0.76 | | | |
| van der Horst [18] | whole blood vs. blood component (not non-MTP) | OR | 0.98 | 0.79 | 1.21 | 0.72 | 0.53 | 0.97 |
| Cruciani [20] | whole blood vs. blood component (not non-MTP) | OR | 0.9 | 0.62 | 1.3 | 0.8 | 0.4 | 1.59 |
| Crowe [19] | whole blood vs. blood component (not non-MTP) | OR | 0.79 | 0.48 | 1.31 | 0.83 | 0.56 | 1.24 |

Table 4: Analysis information

| **Model** | | **Effect size and 95% interval** | | | **Test of null (2-Tail)** | | **Heterogeneity** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Number Studies** | **Point estimate** | **Lower limit** | **Upper limit** | **Z-value** | **P-value** | **Q-value** | **df (Q)** | **P-value** | **I-squared** |
| **Mortality (30-day mortality and in-hospital mortality)** | | | | | | | | | | |
| **Fixed** | 5.00 | 0.654 | 0.578 | 0.741 | -6.661 | 0.000 | 1.275 | 4 | 0.886 | 0.00 |
| Random effects | 5.00 | 0.654 | 0.578 | 0.741 | -6.661 | 0.000 | | | | |
| **24-h mortality** | | | | | | | | | | |
| **Fixed** | 3.00 | 0.763 | 0.608 | 0.957 | -2.335 | 0.020 | 0.332 | 2.00 | 0.847 | 0.00 |
| Random effects | 3.00 | 0.763 | 0.608 | 0.957 | -2.335 | 0.020 | | | | |

Table 5: JBI critical apprasial for systematic reviews.

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| van der Horst [18] | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | No | Yes | Yes | 9 |
| Bhangu [25] | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | 9 |
| Johansson [14] | Yes | Yes | Unclear | Yes | No | Unclear | Unclear | Yes | No | Yes | Yes | 6 |
| Patel [26] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | 10 |
| Kang [27] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 11 |
| Carson [28] | Yes | Yes | Unclear | Yes | Yes | No | Yes | Yes | No | Yes | Yes | 8 |
| Murad [29] | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | No | Yes | Yes | 9 |
| Stanworth [30] | Yes | Yes | Unclear | Yes | Yes | Unclear | No | Yes | Not applicable | Yes | Yes | 7 |
| Phan [31] | Yes | Yes | Unclear | Yes | No | Unclear | No | Yes | Not applicable | Yes | Yes | 6 |
| Curry [13] | Yes | Yes | Unclear | Yes | Yes | Unclear | Yes | Yes | Not applicable | Yes | Yes | 8 |
| Langenecker [32] | Yes | Yes | Yes | Yes | Unclear | No | Unclear | Yes | Not applicable | Yes | Yes | 7 |
| Rajasekhar [1] | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Not applicable | Yes | Yes | 9 |
| Vogt [17] | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | 9 |
| Hallet [33] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Yes | Yes | 10 |
| Mitra [15] | Yes | Yes | Unclear | Yes | Yes | Unclear | Unclear | Yes | No | Yes | Yes | 7 |
| McQuilten [34] | Yes | Yes | No | Yes | Unclear | Yes | Yes | Yes | Not applicable | Yes | Yes | 8 |
| Smith [35] | Yes | Yes | Unclear | Yes | yes | Unclear | Unclear | Yes | No | Yes | Yes | 7 |
| Tanaka [11] | Yes | Yes | Unclear | Yes | Yes | Unclear | Unclear | Yes | Not applicable | Yes | Yes | 7 |
| Teodoro da Luz [22] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | 10 |
| Kamyszek [36] | Yes | Yes | Unclear | Yes | No | Yes | Unclear | Yes | Not applicable | Yes | Yes | 7 |
| Rijnhout [37] | Yes | Yes | Unclear | Yes | Yes | Yes | No | Yes | No | Yes | Yes | 8 |
| Shand [38] | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Not applicable | Yes | Yes | 8 |
| Sommer [16] | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | No | Yes | Yes | 8 |
| Avery [39] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Not applicable | Yes | Yes | 10 |
| Consunji [8] | Yes | Yes | Unclear | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | 9 |
| Crowe [19] | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Kinslow [12] | Yes | Yes | Yes | Yes | No | No | Unclear | Yes | Not applicable | Yes | Yes | 7 |
| Ritchie [40] | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Not applicable | Yes | Yes | 8 |
| Rodrígueza [41] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 11 |
| Cruciani [20] | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Unclear | Yes | Yes | 10 |
| Malkin [42] | Yes | Yes | Unclear | Yes | Yes | Yes | Unclear | Yes | Not applicable | Yes | Yes | 8 |
| Jones [43] | Yes | Yes | Unclear | Yes | Yes | Yes | No | Yes | Not applicable | Yes | Yes | 8 |

Q1: Is the review question clearly and explicitly stated? Q2: Were the inclusion criteria appropriate for the review question? Q3: Was the search strategy appropriate? Q4: Were the sources and resources used to search for studies adequate? Q5: Were the criteria for appraising studies appropriate? Q6: Was critical appraisal conducted by two or more reviewers independently? Q7: Were there methods to minimize errors in data extraction? Q8: Were the methods used to combine studies appropriate? Q9: Was the likelihood of publication bias assessed? Q10: Were recommendations for policy and/or practice supported by the reported data? Q11: Were the specific directives for new research appropriate?

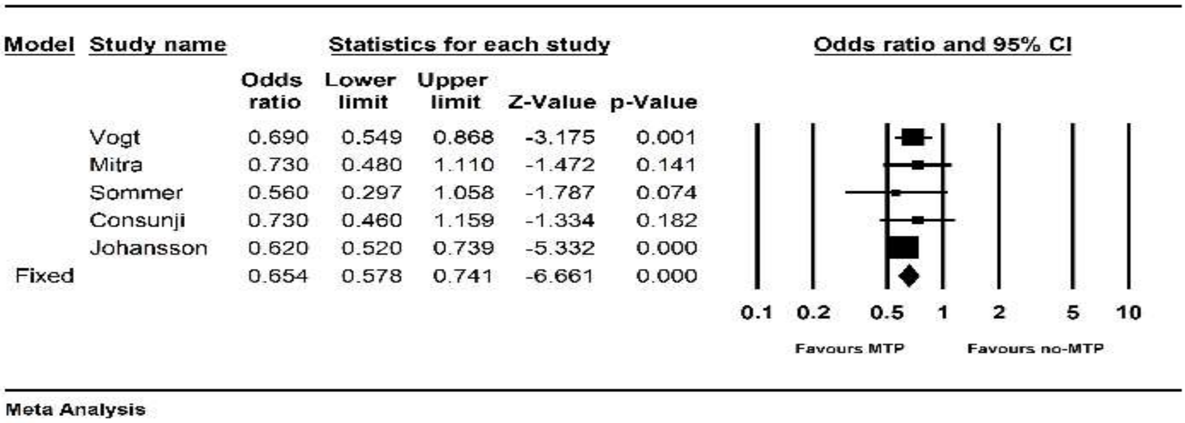


Figure 2: Forest plot 30-day mortality (MTP vs. non-MTP

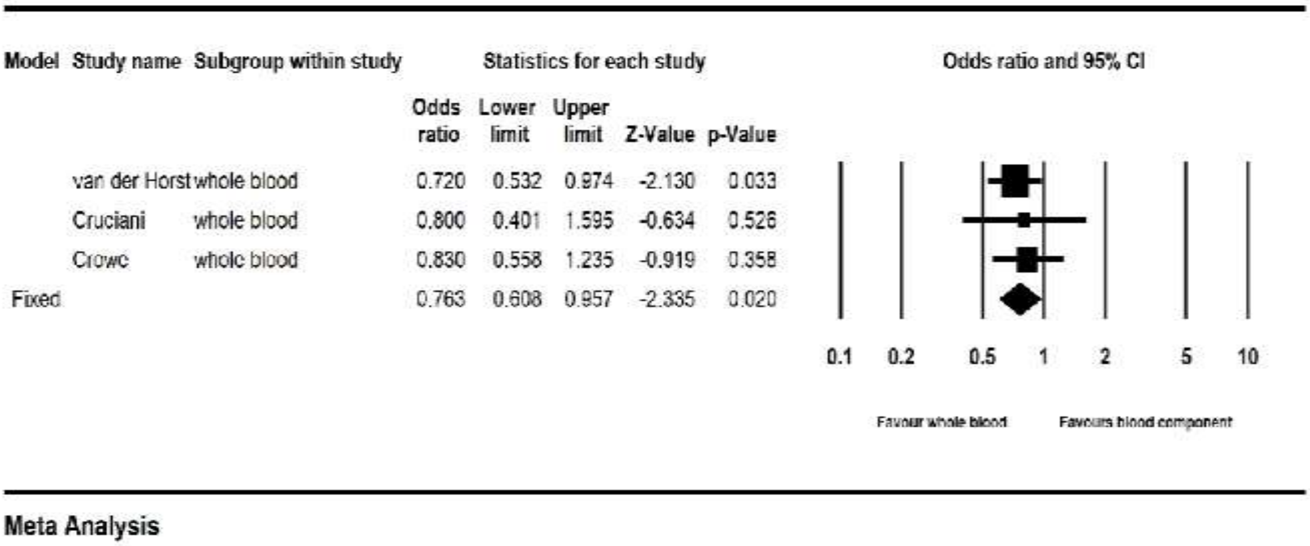


Figure 3: forest plot 24h-mortality (whole blood vs. blood components)

## Discussion

This umbrella review summarized the clinical evidence of MT on 24h- mortality and 30-day mortality in trauma and non-trauma patients. Of a total of 5633 initial articles retrieved, 30 eligible systematic reviews were included, and eight studies were eligible to be included in the meta-analysis. The included studies were conducted in 12 countries, involved various patient populations (military trauma, civilian trauma, non-trauma), and reported on different blood transfusion strategies (MTPs, whole blood, FFP: RBC, PLT: RBC). Ten studies found that a high ratio of FFP: RBC and PLT: RBC reduced mortality, while four studies reported no difference in mortality with whole blood transfusion. Three studies evaluated prehospital blood transfusion and found no difference in mortality. Several side effects were reported after transfusion, including ARDS, AKI, MOF, sepsis, pneumonia, thrombotic events, allergic reactions, acute lung injury, and transfusion-associated circulatory overload. The meta-analysis of 8 studies found that MTPs were associated with lower 30-day and in-hospital mortality compared to non-MTP groups. However, the association with 24-hour mortality was less consistent.

The management of trauma patients with severe bleeding and coagulopathy has undergone significant improvements in the last twenty years. MTPs have been established as therapeutic interventions for addressing the needs of this specific group. Furthermore, within the realm of military observation, the utilization of component treatment involving increased transfusion ratios of FFP and PLTs/ RBCs has demonstrated a notable advantage in terms of survival. At this point, most trauma hospitals employ MTPs designed to facilitate the early resuscitation of a high ratio of FFP and PLTs/ RBC [21, 22].

Regardless of quality, most systematic reviews and meta-analyses stated that a high FFP/Plt: RBC ratio improves survival. Five studies compared the MTP and non-MTP groups, and two of them concluded that MTP decrease the odds of 30-day mortality. However, Consunji et al., in a meta-analysis of fourteen studies, concluded that MTP did not affect 24h-mortality and 30-day mortality (OR 0.81; 95% 0.57-1.14, OR 0.73; 95%, 0.46-1.16). Besides, the authors reported that overall mortality was decreased in the MTP group (OR 0.71, 0.56-0.90). The heterogenicity of trauma patients, not enough standard reports of MTP outcome values, and specified MTP centers were the main limitations of the mentioned article [8]. Similarly, Mitra and colleagues, in a meta-analysis of eight studies and 1587 patients, noted that MTP did not improve survival in patients. The calculated OR was 0.73. 95%[0.48–1.11] [15]. In non-trauma patients, Sommer et al., in the analysis of four studies, showed a trend of lower mortality in the MTP group compared to the non-MTP group [16].

Overall, according to our analysis, MTP decreases 30-day mortality in trauma and non-trauma patients, and the majority of studies reported that a high ratio of FFP/ Plt: RBC improves survival compared to a low ratio of FFP/ Plt: RBC.

For the last decades, whole blood has been used for the treatment of trauma patients, mainly in military settings. The utilization of whole blood transfusion as a therapeutic intervention for managing hemorrhagic shock and coagulopathy in seriously injured individuals has a well-established historical background spanning over a century, with a notable emphasis on its application within military contexts. In recent years, whole blood (WB) transfusion for hemostatic resuscitation has been changed by an alternative approach involving transfusion of blood component products in a balanced ratio. This shift in strategy has been mainly observed in the setting of civilian trauma [23]. Our study observed that 24h-mortality is significantly lower in patients who received whole blood compared to the blood component. No heterogenicity was seen among the included studies. Also, whole blood has a higher FFP/Plt: RBC ratio. The potential cause for the inverse relationship between early PLT/RBC ratios and mortality in the BCT group is the considerably reduced PLT/RBC ratios compared to the WB group. The inverse relationship between plasma/RBC ratio and early mortality indicates that the WB and BCT groups exhibit an advantage in early survival when higher plasma: RBC ratios are utilized [18]—However, Teodoro da Luz et al. in a meta-analysis of 53 observational studies and 2 RCTs.

The included studies for whole blood in 24h-mortality were varied. Cruciani et al., in a meta-analysis of eight studies and 3642 patients, stated that 24h-mortality and 30-day mortality are the same between the whole blood group and blood component in the civilian and military settings, OR 0.80, 95% CIs 0.40, 1.59, and OR, 090, 95% CIs 0.62, 130) [20]. On the other hand, Van der Hort in a civilian and military setting demonstrated that whole blood decreased the odds of 24h-mortality (OR, 0.72; 95% CI, 0.53–0.97) and OR for 24h-mortality and 30-day mortality in a military setting did not differ between the groups [18]. Military logistics cause variations in mortality rates. For instance, extended extrication may worsen the patient's condition; furthermore, military personnel experience a higher incidence of penetrating and explosion injuries in comparison to civilian patients [18, 24].

Strengths and Limitations

This umbrella review and meta-analysis have several strengths, including the comprehensive search strategy, rigorous inclusion criteria, and detailed methodological quality assessment. However, it is important to acknowledge some limitations. The heterogeneity of study populations, interventions, and outcomes can affect the generalizability of the findings. Additionally, the reliance on observational studies may introduce biases and confounding factors.

Despite the increasing use of MTPs, there needs to be more consensus regarding their optimal components, timing, and indications. In addition, by identifying the most effective blood transfusion strategies, patient outcomes are improved, complications are reduced, and resource utilization is optimized. Our findings can inform the development of clinical guidelines and protocols for blood transfusion, ensuring that patients receive appropriate care based on the best available evidence.

## Conclusion

Our umbrella review and meta-analysis provide evidence supporting the use of MTPs in trauma patients. While most studies suggest that MTPs are associated with improved outcomes, particularly in terms of mortality, there is some variability in findings across different studies. Further research is needed to refine MTPs and explore alternative transfusion strategies. By addressing the limitations of existing studies and incorporating the insights from this review, healthcare providers and policymakers can make informed decisions regarding blood transfusion strategies to improve patient outcomes.

### Implications for Healthcare Providers, Users, and Policymakers

· **Healthcare Providers:** The results of this review underscore the importance of implementing MTPs in trauma patients. These protocols can significantly reduce mortality rates and improve overall outcomes. However, it is crucial to tailor the specific components and timing of MTPs to the individual patient's needs based on factors such as the type of trauma, severity of blood loss, and comorbidities.

· **Users:** Patients undergoing blood transfusions should know the potential benefits and risks of different strategies. While MTPs have shown promising results, discussing the potential side effects and complications with healthcare providers is essential.

· **Policymakers:** Our findings provide evidence to support the widespread adoption of MTPs in healthcare systems. Policymakers should consider implementing guidelines and protocols that promote the use of MTPs in appropriate settings. Additionally, investments in research are needed to refine MTPs further and explore alternative transfusion strategies.

### Future Directions

Future research should address the limitations of existing studies. Randomized controlled trials are needed to establish a definitive causal relationship between MTPs and improved outcomes. Furthermore, investigations into the optimal components and timing of MTPs and the identification of patient subgroups that may benefit most from these protocols are warranted. The discrepancies in findings across different systematic reviews and meta-analyses can be attributed to several factors, including:

· **Heterogeneity of Study Populations:** Variations in patient demographics, severity of illness, and underlying comorbidities can influence the outcomes of blood transfusion strategies.

· **Differences in Intervention Definitions:** The specific components and timing of MTPs can vary across studies, making it difficult to compare results directly.

· **Methodological Limitations:** Variations in study design, quality assessment, and statistical analysis can also contribute to discrepancies in findings.

These discrepancies underscore the need for further research to clarify the optimal approach to blood transfusion in different patient populations. While MTPs have shown promise in improving outcomes, it is crucial to tailor these protocols' specific components and timing to the individual patient's needs.

### Recommendations for Future Research

Based on the gaps identified in the literature, we recommend the following areas for future research:

· **Head-to-Head Comparisons:** Randomized controlled trials comparing MTPs to traditional blood transfusion strategies in specific patient populations, such as those with severe trauma or acute bleeding disorders.

· **Subgroup Analyses:** Investigations to identify patient subgroups that may benefit most or leased from MTPs based on factors such as age, type of trauma, severity of blood loss, and comorbidities.

· **Cost-Effectiveness Studies:** Evaluations of the economic impact of MTPs compared to traditional blood transfusion strategies, considering both direct and indirect costs.

· **Long-Term Outcomes:** Studies assessing the long-term effects of blood transfusion strategies on patient quality of life, functional outcomes, and survival.

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## Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

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## Authors' Contributions

K.Sh.: conceptualization, writing and reviewing, project administration, supervision.

K.Sh., H.S.P., H.S.: Data extraction, data analysis, provision of study materials, study validation, data presentation, draft preparation.

K.A., N.H., M.B., S.H.: data presentation, draft preparation, study consultation, writing and reviewing.

All authors approved the final version of manuscript.

## Ethical Statement

This research was confirmed by the ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran, with the ethics code: IR.TBZMED.REC.1401.546.

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