A review and analysis of outcomes in randomized clinical trials of plasma transfusion in patients with bleeding or for the prevention of bleeding, the BEST Collaborative Study

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REVIEW ARTICLE

TRANSFUSION

A review and analysis of outcomes in randomized clinical trials of plasma transfusion in patients with bleeding or for the prevention of bleeding: The BEST collaborative study

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Abstract

Background: Previous systematic reviews have revealed an inconsistency of outcome definitions as a major barrier in providing evidence-based guidance for the use of plasma transfusion to prevent or treat bleeding. We reviewed and

Abbreviations: CFC, coagulation factor concentrate; COMET, Core Outcome Measures in Effectiveness Trials; COS, core outcome set; FFP, fresh frozen plasma; MB-FFP, methylene blue treated fresh frozen plasma; PCC, prothrombin complex concentrate; Q-FFP, quarantine fresh frozen plasma; S/D- FFP, solvent-detergent fresh frozen plasma.

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analyzed outcomes in randomized controlled trials (RCTs) to provide a methodology for describing and classifying outcomes.

Study Design and Methods: RCTs involving transfusion of plasma published after 2000 were identified from a prior review (Yang 2012) and combined with an updated systematic literature search of multiple databases (July 1, 2011 to January 17, 2023). Inclusion of publications, data extraction, and risk of bias assessments were performed in duplicate. (PROSPERO registration number is: CRD42020158581).

Results: In total, 5579 citations were identified in the new systematic search and 22 were included. Six additional trials were identified from the previous review, resulting in a total of 28 trials: 23 therapeutic and five prophylactic studies. An increasing number of studies in the setting of major bleeding such as in cardiovascular surgery and trauma were identified. Eighty-seven outcomes were reported with a mean of 11 (min–max. 4–32) per study. There was substantial variation in outcomes used with a preponderance of surrogate measures for clinical effect such as laboratory parameters and blood usage.

Conclusion: There is an expanding literature on plasma transfusion to inform guidelines. However, considerable heterogeneity of reported outcomes constrains comparisons. A core outcome set should be developed for plasma transfusion studies. Standardization of outcomes will motivate better study design, facilitate comparison, and improve clinical relevance for future trials of plasma transfusion.

KEYWORDS

bleeding, core outcome set, hemorrhage, plasma transfusion, prophylaxis, randomized trials

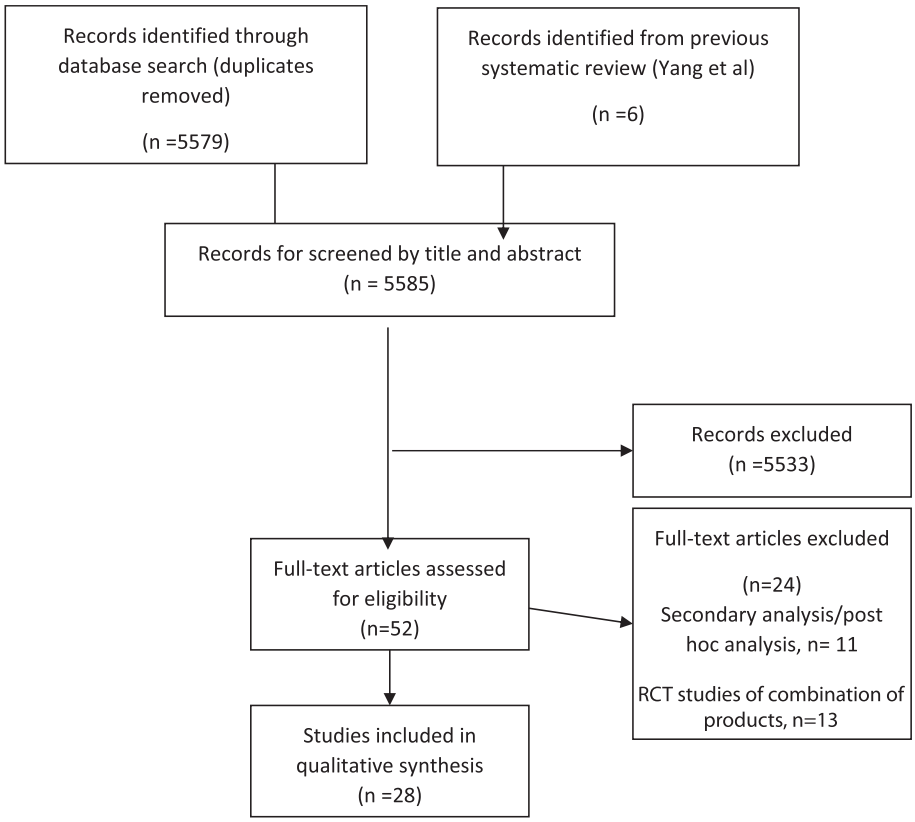
1 | BACKGROUND

Audits of blood use describe diverse indications for plasma transfusion,[1] including burns resuscitation,[2] hemostatic control,[3–5] and more recently as a source of COVID-19 antibodies in convalescent plasma.[6] A recurring common indication for plasma, for nearly 60 years, is as a source of procoagulant factors to prevent bleeding in high-risk settings (prophylaxis) or to treat active bleeding (therapy).[7] There is emerging interest in plasma transfusion for prehospital and inhospital treatment of massive hemorrhage, both for initial hemostatic resuscitation and intravascular volume expansion.[8–12] Indications for the use of plasma continue to be evaluated in randomized controlled trials (RCTs) as collated in systematic reviews.[13,14]

Previous systematic reviews have noted inconsistency in outcome definitions across plasma transfusion trials.[13,14] An outcome is defined as a measurable change in health status, sometimes attributable to a risk factor or an intervention.[15] For research findings to influence medical practice and further research, outcomes should ideally represent a clinically important measure. When surrogate measures are reported, they should be clearly defined and relevant for the disease or condition being investigated. A lack of standardized outcomes can contribute to substantial heterogeneity in reported results, preclude evidence synthesis such as meta-analyses, and limit guideline recommendations for clinical practice.

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative is a recent collaborative effort to develop methods for improving consistency in outcome reporting for clinical trials. COMET recommends the use of core outcome sets (COS) defined as an "agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care."[16,17] The Consensus-based Standards for Selection of Health Status Measurement Instruments (COSMIN) maintains a live database of core outcome sets developed or in development across various diseases and populations, such as renal replacement therapy, post-stroke care, and rheumatoid arthritis management.[18] A COS may offer a way to standardizing clinically relevant outcomes including hemostatic or

FIGURE 1 Overview of inclusions.



bleeding measures for trials of plasma. However, there is currently no COS related to plasma transfusions. The need for consensus and transparency in outcome selection and reporting provides the rationale to develop a COS for clinical trials investigating the effects and safety of plasma transfusion.

The current study has two primary objectives:

1. To undertake a systematic review and provide a narrative summary (including a description of clinical settings, study populations, and indication) of randomized trials of plasma transfusion for the treatment and prevention of bleeding.
2. To create Material and Methods, a list of outcomes which have appeared in past trials for use in developing a core outcome set for future trials evaluating efficacy and safety of plasma transfusion.

1.1 | Data sources for randomized trial literature and search strategy

We sought to have a broad selection of RCTs of plasma transfusion when given either as prophylaxis prior to surgery or invasive procedures, or as a therapeutic intervention. RCTs involving transfusion of plasma for treatment or prevention of bleeding were identified from a prior review (Yang 2012, search dated July 2011) and combined with an updated systematic literature search of multiple databases (search span July 2011 to January 2023) (Figure 1). We extracted information from trials published between January 2000 and January 2023. The review was registered in PROSPERO, the international prospective register of systematic reviews (registration number is: CRD42020158581).

1.2 | Search strategy for the new systematic search

The new search was performed in collaboration with the Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK, using the search strategies from Huber 2019 which focused on plasma use in surgical and invasive procedures.[19] The following databases were included in the search (from January 1, 2011 to January 17, 2023): The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2022, Issue 12); MEDLINE (Ovid); Embase (Ovid); CINAHL (EBSCOhost); PubMed (e-publications and in-process citations ahead of print only); Transfusion Evidence Library (Evidentia Publishing); LILACS (Bireme); and Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters). ClinicalTrials.gov

and the WHO International Clinical Trials Registry Platform (ICTRP) were also searched for ongoing trials.

The search strategy for the systematic search is included in Table S1. The authors also searched references of the identified randomized trials for additional trials missed by the search strategy.

1.3 | Study selection

An overview of the study selection process is presented in Figure 1. RCTs were included in the analysis if they met the following criteria:

1. Plasma transfusions given to adult and pediatric patients either as prophylaxis prior to surgery or invasive procedures, or as a therapeutic intervention (for initial hemostatic resuscitation, supplementation of coagulation factors, and intravascular volume expansion in patients with bleeding).
2. All plasma formulations such as fresh frozen plasma, solvent-detergent treated pooled plasma, pathogen-reduced plasma, and dried or lyophilized plasma.

We included the following comparisons: studies comparing plasma transfusion with standard care or no plasma intervention, studies comparing plasma transfusion with plasma-derived coagulation factors, and studies comparing effect and/or safety of different types of plasma formulations.

RCTs were excluded from analysis if they:

1. Did not explicitly test the effect of plasma alone.
2. If plasma was used for priming of cardiopulmonary circuits, plasma exchange, therapeutic apheresis, convalescent plasma transfusion, and poisonings, as the rationale for use of plasma is different in these contexts.
3. Secondary or post hoc analyses of existing RCTs.
4. Non-English language, nonhuman studies, and in vitro studies of plasma quality.

1.4 | Data collection process

Identification of studies and extraction of data were performed in duplicate by the research team consisting of transfusion medicine professionals and researchers. The titles and abstracts of references retrieved during the systematic search were screened for eligibility by two independent reviewers and full-text articles reviewed at the second stage. Data were abstracted by the research team in duplicate and a qualitative synthesis performed. The following data were extracted: Demographic information on the study (authors, publication year, journal, country of origin); patient population and sample size; details on intervention and comparison; description of outcomes (including specific measurement variable, analysis metric, method of aggregation and presentation of data, time points, core area, and outcome domain); and effect and safety of the intervention (plasma transfusion) for the measured outcomes.

1.5 | Risk of bias assessment

An evaluation of study bias was performed independently by four authors (TOA, SJS, JC, SR) according to the Cochrane Collaboration's Risk of Bias Tool.[20] Each study was assessed by two different authors and ranked on a three-tier scale (yes, no, not reported/uncertain). Assessments included information on randomization method, allocation concealment, baseline differences, blinding methodology, protocol deviations, missing data, blinded adjudication, and outcome reporting. Disagreements in risk-of-bias assessments were resolved through discussion or third-party adjudication.

1.6 | Outcomes

A narrative synthesis was performed to create a comprehensive list of outcomes for further use in development of a COS according to the Core Outcome Set Standards for Development as described in the COS-STAD recommendations,[21] using a systematic transparent process to prepare an initial list of relevant outcomes. The list of outcomes was categorized to consolidate areas of commonality and to map outcome items into core areas and outcome domains according to the taxonomy described by the COMET initiative.[22] Individual outcomes were also further characterized by their outcome measure instruments including analysis metric, method of aggregation, and measurement time points. Both individual and grouped outcomes (such as "adverse events") were included.

1.7 | Statistical analyses

All data including outcomes and their respective measures were extracted into a Microsoft Excel® spreadsheet and descriptive analyses performed. Figures were created using Microsoft Excel and R version 4.2.3 (with iGraph package version 1.5.0).

2 | RESULTS

2.1 | Overall search results

Between July 1, 2011 and January 17, 2023, a total of 5579 citations were identified in the new systematic search and screened for eligibility. Of these, 5533 were excluded based on the title and abstract, and 24 were excluded based on full text, leaving 22 to be included in our analysis. Of the 22 new trials, 19 investigated the efficacy and safety of therapeutic plasma transfusions and three evaluated prophylactic plasma transfusions. For therapeutic plasma transfusion trials, studies of plasma use in cardiovascular surgery ($n = 7$)[3–5,23–26] and trauma ($n = 6$)[9,27–31] were most common, comprising more than half of the included therapeutic trials. Three new prophylactic plasma transfusions trials evaluated the effects of plasma for reversal of a prolonged INR in diverse hospitalized patient settings.[32–34]

For detailed analysis of outcomes, an additional six trials were identified from the previous systematic review by Yang and colleagues, which were published after 2000 and met our eligibility criteria. This resulted in a total of 28 trials to be included in the outcome analysis. Of the 28 included studies, 23 investigated therapeutic plasma transfusions and five investigated prophylactic plasma transfusions. An overview of the inclusions is presented in Figure 1, and demographic information of the included trials is presented in Table 1.

A total of 466 ongoing trials were identified and screened, and six relevant trials (to enroll 1820 additional patients) identified (Table S2) to be incorporated into further iterations of systematic reviews of plasma transfusion.

2.2 | Risk of bias assessment

The risk of bias assessment is shown in Table 2. Many studies were graded as low risk of bias for key domains of randomization methods and allocation concealment. Most studies reported prespecified outcomes and balanced study arms but were unblinded to the clinical team and participants. The number of study participants in most of the studies was low (range, $N = 20$–501).

2.3 | Features of new trials identified in the updated literature search

A narrative summary including a description of clinical settings, study populations, and indication of the 22 plasma transfusion trials identified in the new systematic search is provided below. The results are grouped

TABLE 1 Demographic information on included studies.[a]

	Total ($N = 28$)	Therapeutic studies ($N = 23$)	Prophylactic studies ($N = 5$)
Origin of study			
Europe	13 (46%)	12 (52%)	1 (20%)
North America	7 (25%)	6 (26%)	1 (20%)
Asia	6 (21%)	5 (22%)	1 (20%)
Oceania	1 (4%)	0 (0%)	1 (20%)
Multinational	1 (4%)	0 (0%)	1 (20%)
Year published			
2000–2009	5 (18%)	3 (13%)	2 (40%)
2010–2019	17 (61%)	15 (65%)	2 (40%)
2020–2023	6 (21%)	5 (22%)	1 (20%)
Design			
Multicenter RCT	9 (32%)	6 (26%)	2 (40%)
Single center RCT	19 (68%)	17 (74%)	3 (60%)
Age of study population			
Adults ≥18 years	24 (86%)	19 (83%)	5 (100%)
Children <18 years	3 (11%)	3 (13%)	0 (0%)
Both adults and children	1 (4%)	1 (4%)	0 (0%)

[a]Results given as number (%).

TABLE 2 Risk of bias assessment.

Indication	Category	Study	Allocation random?	Allocation concealed?	Baseline differences?	Participants blinded	Carers blinded?	Protocol deviations?	Missing outcomes?	Outcome assessors blinded?	Selective reporting?
Therapeutic	Surgery	Bartelmaos et al. (2013)	low	low	low	low	low	high	high	high	low
Therapeutic	Surgery	Green et al. (2020)	low	low	low	high	high	high	high	high	low
Therapeutic	Surgery	Karkouti et al. (2021)	low	low	low	low	high	high	low	low	high
Therapeutic	Surgery	Lancé et al. (2012)	low	low	low	low	high	low	low		low
Therapeutic	Surgery	Massoumi G et al. (2018)	low	high	low				low	high	high
Therapeutic	Surgery	Morrison et al. (2019)	low	low	low	low	high	low	low	high	high
Therapeutic	Surgery	Pieters et al. (2015)	low	low	low	low	high	high	high	high	high
Therapeutic	Surgery	Smith et al. (2022)	low	low	high	low	high	low	high	high	low
Therapeutic	Surgery	Stensballe et al. (2018)	low	low	high	low	high	low	low	low	low
Therapeutic	Surgery	Tamura et al. (2020)	low	low	low	high		low	low	high	high
Therapeutic	Surgery	Bindi et al. (2013)	high	high	low	high	high		low	high	low
Therapeutic	Surgery[a]	Chong Sung et al. (2006)			low	high	high	low	low	high	low
Therapeutic	Surgery[a]	Tollofsrud et al. (2003)	low	low	high	high	high	high	low	low	low
Therapeutic	Trauma	Jost et al. (2022)	low	low	high	high	high	high	high	high	low
Therapeutic	Trauma	Moore et al. (2018)	low	low	high	low	high	high	high	high	high
Therapeutic	Trauma	Sperry et al. (2018)	high	high	high	high	high	high	low		low
Therapeutic	Trauma	Zhang et al. (2019)	low	low	low	low	low	low	low	low	high

TABLE 2 (Continued)

Indication	Category	Study	Allocation random?	Allocation concealed?	Baseline differences?	Participants blinded	Carers blinded?	Protocol deviations?	Missing outcomes?	Outcome assessors blinded?	Selective reporting?
Therapeutic	Trauma	Garrigue et al. (2017)	low	low	high	high	high	high	high	low	low
Therapeutic	Trauma	Innerhofer et al. (2017)	low	low	low	low	low	high	low	high	low
Therapeutic	Trauma[a]	Etemadreziae et al. (2007)	low	low	low	low	low		low	low	low
Prophylactic	Prolonged INR	Carson et al. (2021)	low	high	low	high	high	high	high	high	low
Prophylactic	Prolonged INR	Goldstein et al. (2015)	low	low	low	high	high	high	low	high	low
Prophylactic	Prolonged INR	Müller et al. (2015)	low	low	high	high	high	high	low	high	low
Therapeutic	Prolonged INR	Steiner et al. (2016)	low	low	low	high	high	high	low	low	low
Therapeutic	Prolonged INR	Sarode et al. (2013)	low	low	low	high	high	high		low	low
Prophylactic	Prolonged INR[a]	French et al. (2003)		high		high	high	low	low	high	low
Prophylactic	Prolonged INR[a]	Yiu et al. (2006)	high	high	low	high	high	low	low	high	low
Therapeutic	Prolonged INR[a]	Demeyere et al. (2010)	low	low	low	high	high	high	low		

[a]Study included in Yang et al. (2012). Colors denote risk of bias by Cochrane tool (green = low risk; red = high risk; black = unclear risk, not reported).

into the following three categories based on the main indications for plasma transfusion: surgery, trauma, and correction of prolonged International Normalized Ratio (INR).

2.3.1 | Surgery

We identified 11 new trials evaluating the therapeutic effect of plasma transfusion in patients undergoing surgical intervention. Seven studies evaluated the use of plasma transfusion in cardiovascular surgery, two in liver transplantation, and two in other surgical patient populations.

Cardiac and vascular surgery

Seven new randomized trials evaluating plasma for treatment of bleeding in patients undergoing cardiovascular surgery were identified.[3–5,23–26] These trials reported on a total of 505 patients in the setting of cardiac and vascular surgery: five trials in cardiac surgery and two trials in vascular surgery. The trials were heterogeneous in terms of the comparators to fresh frozen plasma including prothrombin complex concentrate (three trials),[3–5] fibrinogen concentrate (two trials),[23,24] and solvent detergent treated plasma (one trial).[25] One additional trial compared the timing of plasma in patients undergoing cardiac surgery (during cardiopulmonary bypass vs. after separation from cardiopulmonary bypass).[26]

Three randomized trials in patients undergoing cardiac surgery compared plasma to prothrombin complex concentrate and reported similar outcomes between the study arms.[3–5] The first trial randomized 50 patients to plasma (15 mL/kg) or prothrombin complex concentrate (500 IU if <60 kg; 1000 IU if 61–90 kg; 1500 IU if >90 kg).[3] Hemostatic, transfusion, and safety outcomes were reported to be similar between the two arms of the study. The second trial randomized 101 patients to plasma (15 mL/kg) or prothrombin complex concentrate (1500 IU if <60 kg; 2000 IU if ≥60 kg).[4] Patients randomized to prothrombin complex concentrate had lower chest tube volumes at 12 and 24 h and were transfused with fewer allogeneic blood products and red blood cell units, as compared to the plasma group. Safety outcomes and the number of thromboembolic events were similar between the two groups. The third trial randomized 100 patients to plasma (15 mL/kg) or prothrombin complex concentrate (15 IU/kg; median dose 1187 IU).[5] Hemostatic, transfusion, and safety outcomes were similar between the two arms.

Two randomized trials compared plasma to fibrinogen concentrate.[23,24] The first study compared plasma (15 mL/kg) to fibrinogen concentrate (40 mg/kg) in 20 adult patients undergoing thoraco-abdominal aortic aneurysm repair to prevent and/or treat hypofibrinogenemia (FIBTEM A10 <8 mm).[23] The total number of allogeneic blood units transfused was higher in the plasma group (11.5 (14–28) versus 4.5 (3–11) units; $p = .011$), when compared to the fibrinogen group. Blood loss and safety outcomes were similar between groups. The second study compared prophylactic administration of plasma (10 mL/kg), as compared to fibrinogen concentrate (70 mg/kg), in 90 pediatric patients undergoing congenital heart surgery.[24] Patients randomized to fibrinogen had lower volumes of blood loss in the first 24 h and similar transfusion and safety outcomes.

One trial randomized 57 adult patients undergoing repair of an aortic dissection on cardiopulmonary bypass to a pathogen-reduced plasma, Octaplas (Octapharma), or plasma.[25] Patients administered Octaplas had lower blood loss estimates, received fewer platelet transfusions, lower volume of all blood products, received less rescue hemostatics (fibrinogen concentrate, recombinant factor VIIa, prothrombin complex concentrate, or cryoprecipitate), and had a shorter ventilation time, when compared to the plasma group. There were no differences in safety measures.

Tamura et al. randomized 30 adult patients undergoing cardiac surgery to the administration of plasma before, as compared to after, separation from cardiopulmonary bypass.[26] The administration of plasma prior to the end of cardiopulmonary bypass did not improve any patient or laboratory outcomes.

Liver transplantation

Two trials were identified in the updated search which evaluated different formulations of plasma in the setting of liver transplantation and bleeding.[35,36] Bartelmaos et al. randomized patients undergoing liver transplantation ($n = 293$) to one of the following three treatment arms administering: quarantine-stored (Q-FFP), methylene-blue treated (MB-FFP), or solvent/detergent treated (S/D-FFP) plasma. The study intended to establish the potency of the three products for improving coagulation. Results showed an excess transfusion volume was required with MB-FFP (2254 mL) when compared to Q-FFP (1798 mL). S/D-FFP (1905 mL) and Q-FFP were equivalent. Quarantine stored plasma was associated with fewer units transfused. There was no significant difference for coagulation parameters or calculated surgical blood loss between the three arms. In a trial of patients undergoing liver transplantation, Bindi et al. prospectively randomized patients to thromboelastography guided fresh frozen plasma or solvent-detergent plasma ($n = 63$). Both study arms equally achieved thromboelastography goals but with a reduced number of

transfusions in the S/D plasma group. At the end of surgery, coagulation factors levels were lower in the S/D plasma group. The study did not examine clinical outcomes.

Other patient populations

Two additional trials were identified describing the use of plasma in the perioperative period. Lancé et al. randomized patients undergoing major elective surgery to receive either four units of fresh frozen plasma ($n = 21$) or two units of fresh frozen plasma plus 2 g of fibrinogen ($n = 17$). The study examined laboratory parameters post-transfusion. The study population included diverse surgical groups (cardiovascular, abdominal, and orthopedic surgery). Compared with fresh frozen plasma, fibrinogen concentrate led to higher fibrin clot formation by ROTEM, and lower thrombin generation by calibrated automated thrombogram. Pieters et al. prospectively randomized children undergoing surgical repair of craniosynostosis to receive fresh frozen plasma plus red blood cells (RBCs) prophylactically (10 mL/kg^{-1} of each product; $n = 40$) or RBCs (10 mL/kg^{-1}) alone, reactively in response to intraoperative bleeding ($n = 39$) and compared downstream laboratory and clinical outcomes. The use of prophylactic plasma in patients undergoing primary repair of craniosynostosis improved coagulation values but was not associated with a change in the RBC transfusion requirement. The prophylactic group received significantly more intraoperative plasma transfusions than the reactive group, and found no difference in blood transfusion requirements, blood loss, pediatric intensive care unit (ICU), or hospital length of stay.

2.3.2 | Trauma

Six new trials examining therapeutic plasma transfusion in the setting of traumatic injury were identified in the updated search.[9,27–31] Of these, three studies evaluated the effect of prehospital plasma transfusion for treatment of trauma-related hemorrhagic shock.[9,29,30]

A total of 953 patients were studied: 194 inhospital studies and 759 in prehospital studies. The trials were heterogeneous in terms of the intervention arm that was compared to plasma: saline (three trials), freeze-dried plasma (two trials), and factor concentrate (fibrinogen concentrate or 4-factor prothrombin complex concentrate; one trial).

Inhospital treatment

The study by Innerhofer et al. aimed to compare the efficacy of first-line therapy for trauma-induced coagulopathy using a single dose of fresh frozen plasma (FFP 15 mL/kg of bodyweight; $n = 44$) or coagulation factor concentrate ($n = 50$; fibrinogen concentrate or 4-factor prothrombin complex concentrate, primarily fibrinogen concentrate dosed as 50 mg/kg of bodyweight). Primary outcomes evaluated transfusion requirements and development of multiple organ failure. The study was terminated early for futility and safety due to a higher proportion of patients in the FFP group needing rescue therapy and massive transfusion. There were no significant differences in the number of patients with multiple organ failure.[27]

Garrigue et al. performed an open-label randomized trial comparing adult trauma patients treated with four units of lyophilized (freeze dried; $n = 24$) or four units of fresh frozen plasma ($n = 24$). Lyophilized plasma led to a more rapid increase in fibrinogen concentrations and coagulopathy improvement compared with FFP in the initial management. Thirty-day inhospital mortality and laboratory parameters of shock (lactate, base excess) did not differ between the two groups.[28]

One trial evaluated the role of plasma transfusion in the treatment of traumatic brain injury. The trial was performed to investigate the role of low-dose, early FFP transfusion (after admission in the operating room; $n = 20$) compared with normal saline ($n = 32$) in preventing perioperative coagulopathy and improving long-term outcome after severe traumatic brain injury in adult patients (mean age, 64.7 ± 8.8 years). The study was terminated early. Lower volume of RBC and FFP transfusion were given, and lower number of delayed traumatic intracranial hematomas were observed in the saline group.[31]

Prehospital plasma transfusion

Three trials examined prehospital plasma administration, enrolling a total of 760 patients. Two trials compared FFP to crystalloid solution, and one compared lyophilized plasma to crystalloid.

Moore et al. performed a prehospital randomized single-center trial comparing two units of FFP ($n = 65$) to normal saline ($n = 60$) in trauma patients with evidence of hemodynamic instability.[9] The groups were similar at baseline and had similar transport times (plasma group median 19 min [IQR 16–23] vs. control 16 min [14–22]). There was no difference in mortality at 28 days (15% in the plasma group vs. 10% in the control group, $p = .37$). There were no significant differences in safety outcomes and adverse events. Sperry et al. performed a pragmatic cluster-randomized multicenter phase-3 trial comparing administration of thawed plasma ($n = 230$) with standard-care resuscitation (crystalloid; $n = 271$) during prehospital air-medical transport. For a smaller proportion of the participating sites additional red cell

concentrates were available. The researchers found that prehospital plasma transfusion was safe and showed a mortality benefit at 30 days after randomization (23.2% vs. 33.0%; absolute difference: −9.8%; 95% confidence interval: −18.6 to −1.0%; $p = .03$).[12] A third trial by Jost et al. randomized adults at risk of trauma-induced coagulopathy to receive either lyophilized plasma ($n = 68$) or standard of care normal saline infusion ($n = 66$). Coagulopathy risk was considered high in those with shock index greater than 1.1, or initial systolic BP less than 70 mmHg. The trial demonstrated no difference in INR, need for massive hemorrhage protocol, or 30-day survival.[29]

2.3.3 | Use of plasma to correct prolonged International Normalized Ratio

Five new trials were identified in the updated search in which prolonged INR was described as the indication for transfusion.[32–34,37,38] The rationale for the use of plasma for correction of prolonged INR is to treat coagulopathy caused by reduced levels of important coagulation factors to reduce risk of bleeding, or as supplementary treatment of patients with bleeding due to low levels of coagulation factors. Three studies evaluated the effect of prophylactic plasma transfusion for coagulation factor supplementation in patients in relation to, or before, undergoing procedures,[32–34] and two studies examined plasma as a therapeutic intervention in cohorts of bleeding patients with prolonged INR due to Vitamin K antagonists.[37,38]

Prolonged INR in non-bleeding patients

The three identified trials evaluating the use of plasma transfusion for correction of prolonged INR in non-bleeding patients varied with respect to the comparator arm: prothrombin complex concentrate (one trial) and to no treatment (two trials). Two of the studies investigated patients with prolonged INR due to Vitamin K antagonists[33,34] and one trial investigated hospitalized patients with multiple of etiologies for prolonged INR.[32] A total of 318 patients were studied.

A multicenter phase-3 trial compared four-factor prothrombin complex concentrate to FFP for adults ($n = 181$) therapeutically anticoagulated on warfarin requiring urgent surgical or invasive procedures. The study showed non-inferiority for prothrombin complex concentrate with respect to INR reversal, intraoperative blood loss, and hemostatic interventions. Safety profiles were reported as being similar, however, a higher number of patients with fluid overload or similar cardiac events were reported in the patients receiving plasma as compared to 4F-prothrombin complex concentrate (13 vs. 3%).[33]

Two studies were performed in patients with prolonged INR with different etiologies. An open-label trial examined the use of prophylactic FFP in critically ill patients ($n = 81$) with prolonged INR, specifically excluding patients treated with Vitamin-K antagonists. The patients were undergoing invasive nonsurgical procedures (central venous catheterization, percutaneous tracheostomy, chest tube insertion, or abscess drainage). Authors compared prophylactic FFP to no treatment. Treatment with FFP resulted in a reduction of INR to below 1.5 in 54% of cases. There was no difference in bleeding complications or lung injury scores between the groups.[34]

A pilot trial including hospitalized patients with prolonged INR undergoing procedures randomly allocated adults ($n = 57$) to receive plasma transfusion ($n = 27$, 10–15 mL/kg) or no transfusion ($n = 30$). The authors found no effect on the primary outcome of hemoglobin concentration between the two groups. No difference in safety outcomes was reported.[32]

Reversal of prolonged INR due to Vitamin K antagonists in patients with bleeding

Two trials were identified that examined plasma as a therapeutic intervention in bleeding patients.[37,38] Both trials investigated the use of plasma transfusion for reversal of Vitamin K antagonists in bleeding patients, as compared to prothrombin complex concentrate. A total of 254 patients were studied.

Sarode et al. performed a multicenter open-label phase III trial which randomized patients on vitamin K antagonist therapy and experiencing an acute major bleeding event. The patients received either 4-factor prothrombin complex concentrate ($n = 98$) or plasma ($n = 104$) for reversal of anticoagulation (dose based on baseline INR and body weight). In the intention-to-treat population, the trial demonstrated non-inferiority for effective hemostasis and superiority for rapid INR reduction in patients receiving 4F-prothrombin complex concentrate. No significant differences were reported in safety outcomes.[37]

In a multicenter randomized open-label trial, patients with intracranial bleeding on vitamin K antagonists ($n = 54$) were randomized to receive FFP (20 mL/kg) ($n = 26$) or prothrombin complex concentrate (30 IU/kg) ($n = 28$). Compared with FFP, patients with prothrombin complex concentrate had higher odds of reaching target INR (1.2) and lower odds of hematoma expansion. The trial was ended early due to safety concerns with the use of FFP.[38]

2.4 | Outcome analysis

Information on outcomes was retrieved from studies identified in the new search (July 2011–January 2023) and from the previous systematic review from Yang et al. (September 2002–July 2011).[14] A wide variety of outcomes and categories of outcomes were identified both for studies of therapeutic and prophylactic plasma transfusion (Figure 2). The outcomes were sorted into four main groups (clinical, laboratory, resource use, and life impact). Eighty-seven different types of outcomes were reported including clustered outcomes such as adverse events and transfusion reactions, which were mainly reported without giving details on specific types of events/reactions. A total of 296 records of outcomes were registered in the database for the 28 studies. A mean of 11 outcomes were reported for each study with a range from 4 to 32 (min-max) different outcomes per study. When categorized according to the COMET initiative taxonomy table, the following core areas were identified (number and % of total recordings): physiological/ clinical ($N = 149$, 50%), resource use ($N = 84$, 28%), adverse events ($N = 37$, 13%), death ($N = 15$, 5%), and life impact ($N = 11$, 4%). The complete list of outcomes with additional details, including COMET classification by core area, outcome domains, and method of aggregation are presented in Table S3.

Laboratory measures of coagulation (83%) and adverse events (70%) were the most common outcomes used in therapeutic studies. Only 61% of the therapeutic studies reported bleeding as an outcome, whereas blood usage was included as an outcome in 65% of studies. In prophylactic studies, adverse events and INR were most commonly used (Table 3). In summary, the identified studies show a wide variation of outcomes used, with a strong emphasis on the use of laboratory analysis and blood usage as surrogate measures for clinical effect.

We identified several instances where the same reported outcome was operationalized differently across trials. Bleeding for instance was reported as numbers of transfusions required, change in hemoglobin values, volume of chest drain output, volume of intraoperative blood loss, and calculated by a mathematical model for blood loss. The main method of aggregation was number (proportion) of patients and values at specific time points (Table S3). An example of this is number and proportion of patients with bleeding or hemoglobin value at specific time points. The time points used for recording the outcomes also varied both with type of outcomes and within individual outcomes from hours up to 90 days after intervention (data not shown). For bleeding this could be defined as intraoperative, postoperative without specification of time, or it was measures at specific time points as 1, 4, 6, 12, or 24 h after start of intervention.

3 | DISCUSSION

There continues to be substantial research interest in defining the optimal use of plasma for transfusion, as shown by the number of new and ongoing RCTs. Most of the studies are, however, small and the variability in outcome reporting and the inconsistent results for volumes of transfusion requirements preclude comparison and limits interpretation for clinical implication. Studies of plasma use in patients with major bleeding are difficult to perform as early balanced transfusion is recommended for this patient population and imbalances in the use of crystalloids and red cell transfusions are frequent. The influence of other blood products and hemostatic agents complicates the interpretation of the results. Furthermore, timing of administration is important for studying the effect of plasma transfusion. Secondary analysis combining the results from two of the identified prehospital studies shows that differences in patient transport times influence results in prehospital studies.[39] The findings indicate a beneficial effect of plasma transfusion when used as a bridge to balanced blood transfusion for prehospital management of patients with severe bleeding in case of delayed evacuation, major incidents, and war.

Our descriptive analysis of new plasma trials identified a range of issues which have been raised in our previous review.[14] Very few studies have investigated the effect of plasma transfusion versus no treatment, which is the fundamental study design for evaluating the full benefit of plasma transfusion. All new trials undertaken typically addressed a study-specific hypothesis and differed considerably in their method of randomization, nature of intervention (e.g., choice of plasma or procoagulant agents), comparator arms, and reported outcomes. Blinding of plasma transfusion trial interventions is usually not possible, which makes selection of outcomes more important, unless hard clinical endpoints such as mortality are used. There is wide variability in the measurement tools used, methods of aggregation, and timing of outcome assessment.

Overall, we noted a lack of standardized outcomes across trials with an overrepresentation of laboratory measurements or resource use. This raises questions regarding whether many of the trial outcomes were meaningful, relevant, and appropriately powered to improve understanding of the efficacy and safety of plasma transfusion. Careful selection of patient-centered outcomes is crucial to interpreting trial findings and translating into clinical practice.[40] Although expert

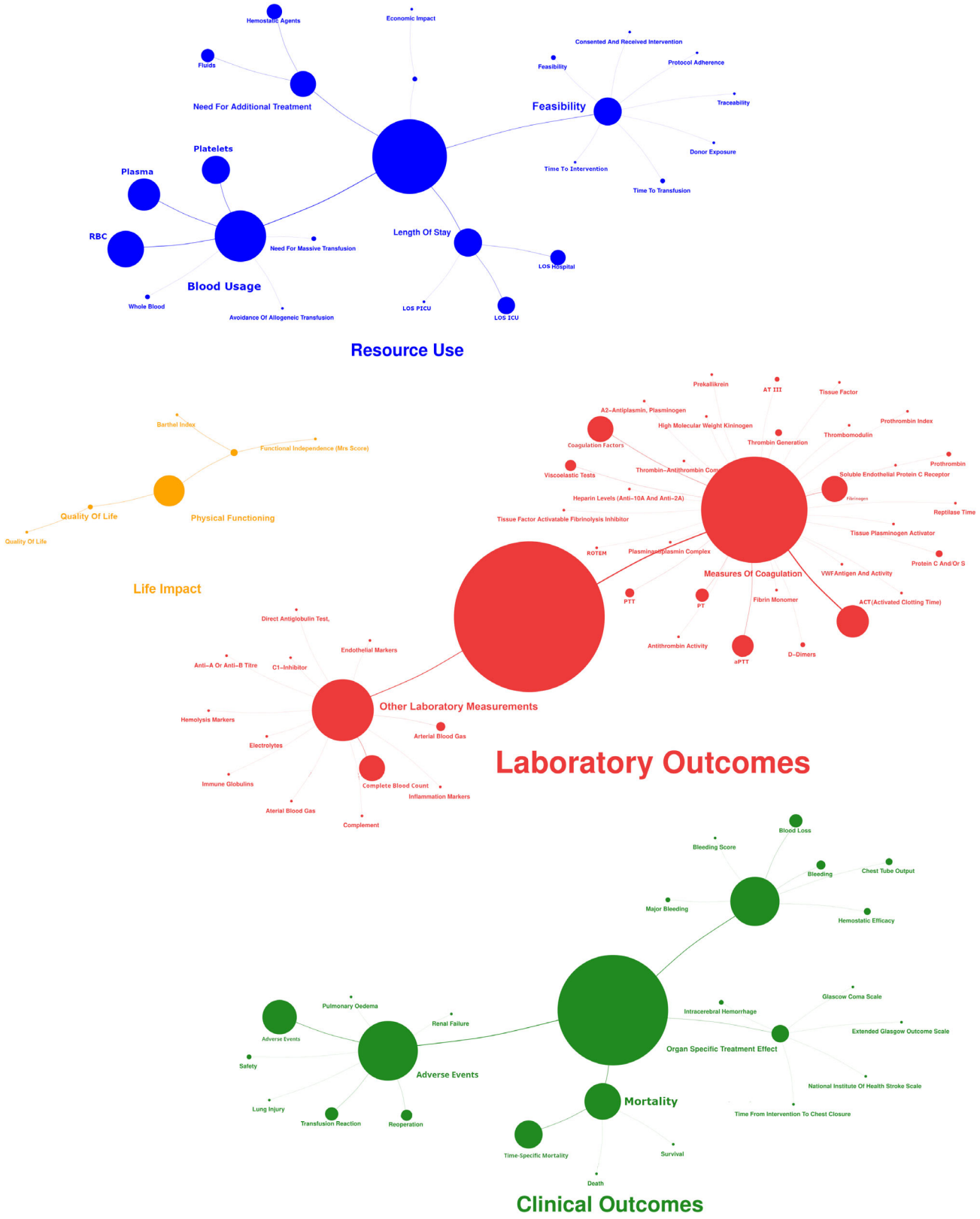


FIGURE 2 Overview of outcomes: weighted network graph depicting categories and individual outcomes reported in randomized controlled trials of plasma therapy classified using core outcome set framework. Vertices represent categories. Edges represent classification hierarchy. Vertex size represents number of studies which reported each category or outcome.

TABLE 3 Overview of outcomes presented in the therapeutic and prophylactic plasma transfusion studies.

	Therapeutic studies ($N = 23$)	Prophylactic studies ($N = 5$)
Clinical outcomes		
Adverse events	16 (70%)	5 (100%)
Bleeding	14 (61%)	3 (60%)
Mortality	13 (57%)	1 (20%)
Organ-specific outcomes	3 (13%)	0 (0%)
Laboratory outcomes		
INR	10 (43%)	5 (100%)
Other measures of coagulation	19 (83%)	3 (60%)
Other laboratory measurements	15 (65%)	1 (20%)
Life impact		
Quality of life	1 (4%)	0 (0%)
Function	1 (4%)	0 (0%)
Resource use		
Blood usage	15 (65%)	2 (40%)
Length of stay	8 (35%)	2 (40%)
Need for additional treatment	9 (39%)	0 (0%)
Feasibility	6 (26%)	0 (0%)
Economic impact	1 (4%)	0 (0%)

Note: Results shown as number (%). Percentage calculated per total for each column.

consensus recommendations have been published on clinical outcomes for trials evaluating the use of blood transfusion (in general) and hemostatic products for treatment of patients with bleeding,[41–44] resulting recommendations were primarily based on expert opinion and did not follow systematic frameworks for outcome selection as descibed in the COS-STAD recommendations. No standardized analysis of outcomes used for trials investigating the effects and safety of plasma has been performed.

The lack of standard measurement tools such as COS measurements also impedes subsequent meta-analysis, thereby reducing the ability to evaluate any effect of plasma interventions via meta-analysis, or to provide standardized guidelines for clinical practice. As a next step, we recommend a Delphi-based consensus process for the development of a COS for studies investigating the use of plasma transfusion in treatment and prevention of bleeding. Core Outcome Set Standards for Development have been described in the COS-STAD recommendations and include defining the scope, identifying relevant stakeholders, and conducting a transparent consensus process.[21]

A potential limitation in our review is that we chose to exclude the studies published before 2000. This was done because there has been a change in transfusion practices in treatment of hemorrhagic shock from year 2000 with implementation of a blood-based resuscitation strategy in contrast to a resuscitation based on clear fluids.[45] We also excluded studies where the separate effect of plasma could not be discerned, for example, the RePHILL-trial which compared administration of RBCs and lyophilized plasma to normal saline.[10] It was not possible to perform a meta-analysis (for the entire dataset or select indications) due to the substantial heterogeneity in analysis metrics, aggregation methods, and time points used for the outcome measures. The list of candidate outcomes we generated based on literature is lacking non-English publications and patient input, and was limited by prevailing laboratory or clinical tools available in the context of where these trials were performed. These issues should be addressed in future efforts to develop a COS. Clinical trials of plasma can be complex to design and interpret, and our study addresses only one aspect of trial design concerning outcome selection.

4 | CONCLUSION

We conclude that there continues to be substantial research interest and need for defining the optimal use of plasma for transfusion especially when used for major bleeding. Our analysis reveals wide variation in outcomes used in randomized plasma transfusion

trials, with an emphasis on surrogate measures for clinical effect. The interpretation of the results regarding efficacy and safety is unclear due to the uncertainty about the clinical relevance of the outcomes used. New study designs would benefit from more consistency in outcome definitions and agreement on relevant standardized core outcome sets, and input from consensus panels. As the next step, we recommend that a transparent consensus process based on the COS-STAD recommendations should be conducted, aimed at defining a core outcome set for future trials investigating the effect and safety of plasma transfusion for treatment or prevention of bleeding. This process can be informed by our initial list of outcomes. Candidate outcomes must be further evaluated and described according to a structured approach using predefined scoring criteria and including a broad representation of stakeholders including healthcare providers, clinical trialists, industry delegates, regulatory bodies, and patient representatives.

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CONFLICT OF INTEREST STATEMENT

The authors declare the following conflicts of interest: TOA has received funding from Innovation Norway for an innovation project related to production of dried plasma. JC received program research support from Canadian Blood Services which produces plasma for transfusion. SR has received fellowship funding from Canadian Blood Service. The other authors declared no potential conflict of interest related to the topic of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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