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Effectiveness of plasma versus crystalloids in pre-hospital hemorrhagic shock: systematic review and meta-analysis

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Abstract

The impact of prehospital plasma transfusion on survival after major trauma remains uncertain. We conducted a systematic review and meta-analysis (PROSPERO CRD420251027516) following PRISMA 2020 standards. Randomized and comparative observational studies published through [March 8, 2025] were included; alerts/hand-searches to April 15, 2025. Primary outcomes were 24-hour and 28–30-day mortality. Pooled Odds Ratios (ORs) were estimated using random-effects models with restricted maximum likelihood and Hartung–Knapp adjustment. Risk of bias was assessed with RoB 2 and ROBINS-I, and certainty of evidence appraised by GRADE. Three randomised trials (n=760) and two observational cohorts were included. Mortality at 28-30 days did not differ between pre-hospital plasma and crystalloids (OR 0.92; 95% CI 0.49-1.72; I^2=50.6%). Twenty-four-hour mortality was not meta-analysed due to heterogeneity. Secondary outcomes showed no clinically significant differences. Observational cohorts were not pooled due to endpoint misalignment and risk of bias. Certainty of evidence ranged from low to very low across outcomes, primarily due to imprecision and inconsistency. Current evidence shows no survival benefit of prehospital plasma over crystalloid resuscitation. The findings remain uncertain, and routine plasma use should be restricted to controlled research or highly structured trauma systems until adequately powered multicenter trials with standardized outcomes confirm benefit. In Emergency Medical Services (EMS) settings, crystalloids remain the pragmatic first-line fluid.

Key words: pre-hospital hemorrhagic shock; plasma; crystalloids; resuscitation; mortality.

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Introduction

Traumatic injuries are a global public health priority, causing about 4.4 million deaths annually (8% of global mortality).[1] Among patients with major trauma, uncontrolled hemorrhage is the leading preventable cause of death, accounting for 30-40% of early fatalities.[2] In the United States, more than 60,000 deaths each year are attributable to traumatic hemorrhage, with an estimated economic burden of US$670 billion.[3] Delays in prehospital management increase mortality;[4] within Europe, national data are available for selected settings – for example, Sweden reports prehospital hemorrhagic mortality of 8.2-11.0 per 100,000 population.[5] Pre-hospital resuscitation has traditionally relied on crystalloids, yet large volumes may exacerbate the "lethal triad" (hypothermia, acidosis, coagulopathy), worsening prognosis.[6,7] Within a Damage Control Resuscitation (DCR) paradigm, early administration of Fresh Frozen Plasma (FFP) or Lyophilized Plasma (LP) is advocated to rapidly restore coagulation factors, limit hemodilution, and maintain oncotic pressure;[7,8] operationally, FFP requires a cold chain and thawing time, whereas LP is stable at ambient temperature and can be rapidly reconstituted – features advantageous when transport times are prolonged.[8] Prehospital teams (nurses, paramedics, physicians) are pivotal for timely vascular access, fluid titration, and surveillance for transfusion reactions.[9] Prior systematic reviews show heterogeneity in study designs and outcomes and uneven application of GRADE (Grading of Recommendations, Assessment, Development and Evaluation);[10-12] moreover, the lack of separate analyses for randomized versus observational studies and nonharmonized assessment times (24 hours and 30 days) limits comparability.[10-12] This systematic review and meta-analysis, conducted in accordance with PRISMA 2020 and the Cochrane Handbook, evaluates whether, in adults with major trauma, prehospital plasma transfusion (FFP or LP), compared with crystalloids, reduces mortality at 24 hours and 28-30 days; secondarily, it examines safety (Transfusion-Related Acute Lung Injury [TRALI], Transfusion-Associated Circulatory Overload [TACO], venous or arterial thromboembolism, sepsis, Multiple Organ Failure [MOF]), hospital Length Of Stay (LOS) and ICU length of stay, subsequent transfusion requirements, and hemostatic parameters on hospital arrival

(International Normalized Ratio [INR], hemoglobin, lactate, platelet count).[13,14]

Materials and Methods

Protocol and reporting standards

This review conformed to PRISMA 2020 and the Cochrane Handbook (v6.3). Protocol registration in PROSPERO (CRD420251027516) occurred April 12, 2025 – post-search (March 8, 2025) but prior to screening, extraction, and analysis. Population, Intervention, Comparator, and Outcome (PICO) elements, outcomes, and statistical analyses were prespecified in a timestamped protocol with no data-driven changes. Deviations are listed in *Supplementary materials, Table A1* (PRISMA item 24c). Because protocol registration followed database searching, AMSTAR 2 item 2 compliance was partial.

Sources and search strategy

We conducted a systematic search of PubMed (MEDLINE), Embase, CINAHL, CENTRAL, and Web of Science without restrictions on study design or publication status.[13,14] All study designs were eligible (AMSTAR 2).[15] The search covered January 1, 2014, to March 8, 2025; articles in English or Italian were included, while other languages were considered if informative abstracts were available, acknowledging possible language bias. Grey literature was searched (ClinicalTrials.gov, ICTRP, medRxiv, OpenAIRE, theses, conference proceedings). The strategy, PRISMA-S compliant,[16] utilized the PICO framework, controlled vocabulary (MeSH, Emtree, CINAHL Headings), and free-text terms, with truncation and proximity operators applied. Complete search strings and PRESS review are reported in *Supplementary materials, Tables A2–A3*.[17]

Eligibility criteria

Eligibility was restricted to randomized trials and comparative observational studies (cohort, case–control) including adults (≥18 years) with major trauma managed prehospital. Interventions were FFP or LP vs. standard crystalloid resuscitation. Major trauma required one or more: Injury Severity Score ≥15; systolic BP <90 mmHg and/or HR >120 bpm; Revised Trauma Score ≤10.[18,19] Trauma definitions followed current templates and guidelines on hemorrhage/coagulopathy.[20,21] Blunt and penetrating injuries, any transport mode, were eligible. Studies had to report ≥1 predefined outcome: co-primary (24h/30-day mortality) or secondary (SAEs, hemostasis, transfusion, organizational metrics). Safety was assessed per international transfusion standards.[22,23] Studies with non-aligned mortality timepoints were summarized narratively. Endpoint selection followed GRADE criteria.[24]

Outcomes and operational definitions

The co-primary outcomes were all-cause mortality at 24 hours and 30 days. When 30-day data were unavailable, we used a 28-30-day window as a prespecified proxy, consistent with prior trauma trials and reviews; sensitivity analyses were restricted to studies reporting exact 30-day values.[20,21] Secondary clinical outcomes included TRALI, TACO, VTE/ATE, sepsis, MOF, LOS and ICU length of stay.[22,23] Surrogate outcomes included hemostatic parameters on hospital arrival (lactate, INR, hemoglobin, platelet count), subsequent transfusion requirements (*e.g.*, Packed Red Blood Cell [PRBC] units within 24 hours), and activation of the Massive Transfusion Protocol (MTP).[7,8,24] Massive Transfusion (MT) was defined as ≥10 PRBC units within 24 hours; the Critical Administration Threshold (CAT) corresponded to ≥3 units within 1 hour. Alternative thresholds were analyzed narratively or in sensitivity analyses to preserve comparability.[25,26] Detailed definitions are provided in the *Supplementary materials, Tables A4-1 and A4-2*.

Study selection and data extraction

Records were deduplicated and screened using Rayyan (Qatar Computing Research Institute).[27] Two reviewers screened independently (κ=0.82 pilot, 0.79 overall; 98% concordance). Full-text eligibility assessment (to May 10, 2025) yielded κ=0.70 and 85% agreement. Data extraction was performed independently and in duplicate using a standardized form capturing study characteristics, outcomes, funding, and conflicts. Medians (Interquartile Range [IQR]) were converted to means (Standard Deviation [SD]) via Wan *et al*.[28] Missing data were coded "not reported." Overlapping populations were merged according to the Cochrane Handbook (section 4.6.1.2).[13] No author contact was required, as published data were complete.

Risk of bias and certainty of evidence

Risk of bias was assessed by RoB 2 (randomized trials) and ROBINS-I (observational studies), both outcome- and analysis-specific, independently and in duplicate (disagreements via consensus/third reviewer).[29,30] RoB 2 domains: randomization, deviations, missing data, outcome measurement, selective reporting; cluster issues noted. ROBINS-I domains: confounding, selection, classification, deviations, missing data, outcome measurement, selective reporting. Ratings: low, moderate, serious/critical risk. Evidence certainty appraised with GRADE (bias, inconsistency, indirectness, imprecision, publication bias). Ratings Started High (RCTs) or low (observational), with upgrade/downgrade as appropriate; managed in GRADEpro. Summary ratings are discussed in the Results section.[13,14,24]

Statistical synthesis

Analyses were conducted in Stata 18.5. Effect sizes for dichotomous outcomes were expressed as Odds Ratios (ORs) with 95% Confidence Intervals (CIs), computed on the log scale and back-transformed. A random-effects model using Restricted Maximum Likelihood (REML) with the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment was applied because of its conservative performance with sparse data.[13] Heterogeneity was quantified by Cochran's Q, I^2, and τ^2, and a 95% prediction interval was reported. For cluster trials, adjusted estimates were preferred; if unavailable, effective sample sizes were recalculated following Cochrane Handbook guidance.[13] Studies with zero events in both arms were summarized narratively, whereas those with one zero arm received a 0.5 continuity correction. Forest plots were oriented such that values >1 favored survival, but all numerical results were expressed as ORs for mortality. Continuous outcomes were not pooled because of inconsistent reporting and measurement units. Subgroup analyses explored blood product type (FFP *vs* LP), trauma mechanism, and setting (civilian *vs* military). Sensitivity analyses excluded high-risk studies, military-only cohorts, and those lacking exact 30-day mortality data. A summary of analytic procedures is provided in *Supplementary materials, Table A5*.

Publication bias and narrative synthesis

Publication bias testing (formal tests, funnel plots, Duval and Tweedie trim-and-fill) was not performed due to <10 studies per out-

come, in accordance with Cochrane guidance.[13] Gray literature and real-time alerts (to April 15, 2025) were included per PRISMA 2020.[13,14] Outcomes unsuitable for meta-analysis were synthesized narratively using SWiM standards.[31] The narrative synthesis addressed: i) effect direction consistency, ii) measurement/timing comparability, iii) robustness via leave-one-out analysis. Clinical importance was assessed qualitatively; grouping and direction-of-effect criteria were predefined (*Supplementary materials, Table A12*).

Results

Study selection

The systematic search (January 1, 2014–March 8, 2025) identified 3,128 records: Embase (1,130), CINAHL (445), PubMed (540), Cochrane CENTRAL (640), and Web of Science (373). After deduplication in Rayyan, 764 duplicates were removed, leaving 2,364 unique citations. Two reviewers independently screened titles and abstracts (κ, 0.79; 98% agreement). Full texts were assessed independently; disagreements were resolved by discussion or, when needed, a third reviewer. Of the 2,364 records, 2,346 were excluded at title/abstract screening. Eighteen full-text articles were assessed; thirteen were excluded for PICO, design, or outcome reasons. Details of excluded full texts and the primary reason for exclusion are reported in *Supplementary Table A6* (PRISMA 2020, item 16b). Five studies were included: three randomized trials and two comparative observational cohorts. The selection process is depicted in Figure 1 (PRISMA 2020).

Characteristics of included studies

Five studies met the inclusion criteria: three Randomized Controlled Trials (RCTs) – COMBAT (Moore *et al.,* 2018), PAMPer (Sperry *et al.,* 2018; cluster randomized), and PREHO-PLYO (Jost *et al.,* 2022) – and two retrospective comparative cohorts (Henriksen *et al.,* 2016; Shlaifer *et al.,* 2019).[34-38] Together, these studies enrolled 1,129 adults with major trauma treated in the prehospital setting. Four were conducted in civilian trauma systems in the United States and France, and one in a military setting in Israel. The intervention was prehospital plasma as part of early Damage Control Resuscitation (DCR), administered as Fresh Frozen Plasma (FFP) in COMBAT, PAMPer, and Henriksen, or as Lyophilized Plasma (LP) in PREHO-PLYO and Shlaifer, and compared with standard crystalloid resuscitation (normal saline or Ringer's lactate). Mortality was reported at twenty-four hours in COMBAT and at twenty-eight to thirty days in COMBAT, PAMPer, and PREHO-PLYO; Henriksen *et al.* and Shlaifer *et al.* reported surrogate or intermediate outcomes that were not amenable to quantitative pooling for mortality.[37,38] Key methodological and operational features are summarized in Table 1.

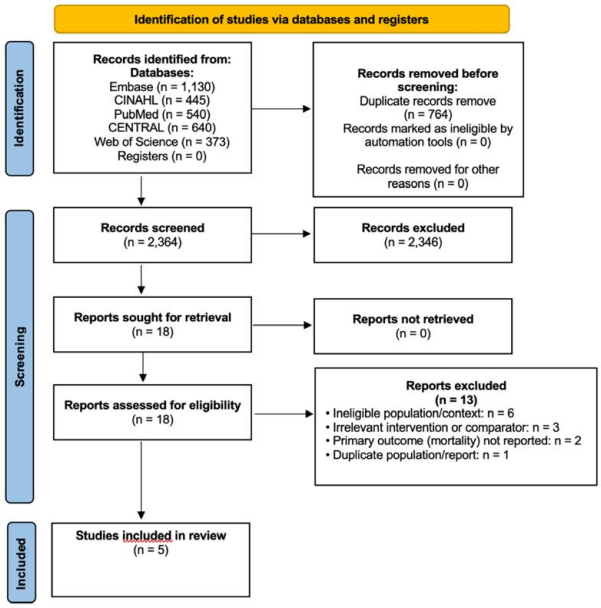

Figure 1. PRISMA 2020 flow diagram of the study selection process. Core search to 8 March 2025; alerts/hand-searching to 15 April 2025.

Table 1. Key characteristics of the five included studies.

Study (year) / Reference	Country	EMS model	Transport	Design and randomization	Intervention (plasma type)	Comparator	N analyzed for 28–30-day mortality (plasma / control)	28–30-day mortality (endpoint)	24-h mortality (endpoint and value)	Funding
Moore 2018 (COMBAT)	USA	Paramedic-based ALS	Ground	Individually randomized (patient)	Fresh frozen plasma (FFP, FP24)	Standard care with crystalloids	65 / 60	28 d reported	Prespecified; 8/65 vs 6/60	U.S. DoD; U.S. Army MRMC
Sperry 2018 (PAMPer)	USA	Paramedic-based ALS	Air	Cluster randomized (air base)	Fresh frozen plasma (FFP)	Standard care without prehospital plasma	230 / 271	30 d primary	Secondary; 13.9% (32/230) vs 22.1% (60/271)	U.S. Army MRMC
Jost 2022 (PREHO-PLYO)	France	Physician-staffed ALS (SAMU)	Ground	Individually randomized (patient)	Lyophilized plasma (LP)	Standard care with crystalloids	66 / 68	28–30 d reported	Descriptive only; 6/66 vs 9/68; not prespecified	French Defence Central Health Service
Henriksen 2016	USA	Mixed (civilian EMS)	Ground/Air	Prospective comparative cohort	Prehospital plasma ± RBCs	Standard care without prehospital plasma	NA / NA	In-hospital only	Not reported	None declared
Shlaifer 2019	Israel	Military EMS	Mixed	Retrospective matched cohort	Lyophilized freeze-dried plasma (FDP)	Standard care without prehospital plasma	NA / NA	In-hospital only	Not reported	IDF Medical Corps; IMOD DDR&D

ALS, advanced life support; EMS, emergency medical services; HEMS, helicopter emergency medical service; GEMS, ground emergency medical service; FFP, fresh frozen plasma; FP24, plasma frozen within 24 hours; LP, lyophilized plasma; FDP, freeze dried plasma; RBCs, red blood cells; ITT, intention to treat; mITT, modified intention to treat; DoD, Department of Defense; MRMC, U.S. Army Medical Research and Materiel Command; SAMU, Service d'Aide Médicale Urgente; 24 h, 24 hours; 28 d, 28 days; 30 d, 30 days; 28 to 30 d, 28 to 30 days; USA, United States of America

Methodological quality of eligible studies

Risk of bias for RCTs was assessed using RoB 2 and for observational studies using ROBINS-I, per Cochrane guidance. Assessments were performed independently and in duplicate; disagreements were resolved by consensus or third reviewer as needed. Judgments followed the Cochrane signaling framework (Table 2). COMBAT (Moore *et al*, 2018)[34] showed some concerns regarding baseline imbalances, unclear allocation concealment, and partial non-adherence; PAMPer (Sperry *et al.*, 2018)[35] and PREHO-PLYO (Jost *et al.*, 2022)[36] had similar concerns for randomization and deviations from intervention. No RCT was rated high risk for outcome measurement or reporting. Henriksen *et al.* (2016)[37] and Shlaifer *et al.* (2019)[38] were at serious risk of bias, mainly for confounding and participant selection; in Shlaifer, unblinded outcome assessment introduced further measurement bias. The distribution of domain-level judgments is shown in Table 2; visualizations and detailed frequencies are in *Supplementary materials, Tables A7–A8*.

Twenty-four-hour mortality

Study-level extraction showed that 24-hour endpoints were not comparable across the three RCTs and were therefore not pooled. In COMBAT (2018) the 24-hour mortality is explicitly reported (8/65 vs 6/60; OR 1.23; 95% CI 0.45–3.34).[34] In PAMPer (2018), a cluster RCT, it appears as a secondary endpoint and is reported only as per-arm percentages (13.9% *vs* 22.1%).[35] In PREHO-PLYO (2022) it is presented descriptively ("within 24 h": 6/66 *vs* 9/68) and is not prespecified in primary efficacy analyses.[36] Operational reasons for non-pooling (non-uniform time zero, non-standardized endpoints/denominators, and cluster design) are provided in *Supplementary materials, Table A9-1*. For completeness, we performed an exploratory sensitivity analysis restricted to trials with operationally usable reporting (COMBAT + PAMPer; k=2), using log risk ratios, REML with Hartung–Knapp, and cluster-adjusted input for PAMPer; results (*Supplementary materials, Table A9-2*) did not change the overall interpretation and remained consistent with no clear 24-hour effect.

Mortality at 28–30 days

Mortality at 28–30 days (a prespecified proxy for 30-day mortality) was consistently reported by COMBAT (Moore *et al.,* 2018), PAMPer (Sperry *et al.,* 2018), and PREHO-PLYO (Jost *et al.,* 2022).[34-36] A Random-Effects Model (REML) with Hartung–Knapp–Sidik–Jonkman adjustment yielded a pooled OR for plasma *vs* crystalloids of 0.92 (95% CI 0.49–1.72; n=760). Between-study heterogeneity was moderate (I^2=50.6%, τ^2=0.16), and the 95% prediction interval (0.35-2.43) indicated substantial uncertainty, with potential effects ranging from benefit to harm. Trial-specific estimates were heterogeneous: PAMPer suggested lower mortality with plasma (OR 0.61, 95% CI 0.41–0.92), PREHO-PLYO was inconclusive (OR 1.19, 95% CI 0.33–4.27), and COM-

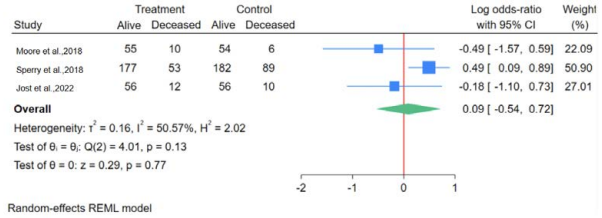

Figure 2. Forest plot of 28 to 30 day mortality (proxy for day 30). OR, odds ratio; CI, confidence interval; REML, restricted maximum likelihood; HKSJ, Hartung Knapp Sidik Jonkman. Plot displayed on the survival scale; values >1 favor survival. Numerical summaries in the text and tables refer to mortality (OR_mortality, 1/OR_survival). To avoid ambiguity, forest plots are presented on the mortality scale (OR < 1 favors plasma), consistent with textual and tabular reporting.

Table 2. Risk of bias by domain for the five included studies.

Study (year)	Tool	D1 Randomization / Confounding †	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall judgment
Moore — 2018 (COMBAT, individual)	RoB 2	Some concerns	Some concerns	Low	Low	Low	Some concerns
Sperry — 2018 (PAMPer, cluster)	RoB 2	Some concerns	Some concerns	Low	Low	Low	Some concerns
Jost — 2022 (PREHO-PLYO)	RoB 2	Low	Some concerns	Low	Low	Low	Some concerns
Henriksen — 2016	ROBINS-I	Serious (confounding)	Moderate (selection)	Low	Moderate (measurement)	Moderate (reporting)	Serious
Shlaifer — 2019	ROBINS-I	Serious (confounding)	Moderate (selection)	Low	Moderate (measurement)	Serious (reporting)	Serious

†For ROBINS-I, D1 corresponds to bias due to confounding. Legend (abbreviations): RoB 2, Risk of Bias 2; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; RCT, randomized controlled trial. Note: Detailed domain-level judgments are presented in *Supplementary Tables A7–A8.*

Table 3. Randomized trials: 28–30-day mortality (primary pooled endpoint).

Study	Patients Plasma/Control	Events Plasma/Control	OR (95% CI)	Survival Effect	Study Design	Time-zero Definition	Transport Time (min)	Plasma Type
COMBAT (2018)	65 / 60	21 / 18	1.64 (0.56–4.82)	Possible harm	Individual RCT	Prehospital randomization	16–22	Standard FFP
PAMPer (2018)	230 / 271	33 / 58	0.61 (0.41–0.92)	Survival benefit	Cluster RCT	Prehospital randomization (cluster)	31–70	Standard FFP
PREHO-PLYO (2022)	68 / 66	16 / 14	1.19 (0.33–4.27)	Inconclusive	Individual RCT	Hospital arrival	≥30	Lyophilized plasma

Legend (abbreviations). OR values refer to 28–30-day mortality (meta-analysis primary endpoint). Events" are deaths at 28–30 days Survival effect interprets the direction suggested by each trial's OR, Main differences (study design, time-zero, plasma type, timelines) summarized for context.

BAT suggested possible harm (OR 1.64, 95% CI 0.56–4.82).[34-36] Differences in design, transport modality, plasma formulation, and prehospital timelines likely contributed to variability (see Table 3 and Figure 2).

Sensitivity and subgroup analyses (28–30-day mortality)

Leave-one-out analyses confirmed the robustness of the pooled estimate (overall OR 0.92, 95% CI 0.49–1.72). Excluding COMBAT: OR 0.84 (95% CI 0.45–1.57; I^2=45.3%). Excluding PAMPer: OR 1.15 (95% CI 0.64–2.06; I^2=0%). Excluding PREHO-PLYO: OR 0.71 (95% CI 0.33–1.53; I^2=0%). Full results are provided in *Supplementary Table A10-1*. Descriptive subgroup analyses were limited by the small number of studies and showed no reproducible trends; observed heterogeneity likely reflects plasma formulation, transport setting, trial design, and prehospital timing (*Supplementary materials, Table A10-2*).

Studies not amenable to meta-analysis

Two cohort studies, Henriksen *et al.* (2016) and Shlaifer *et al.* (2019), reported in-hospital mortality endpoints misaligned with the RCTs and were excluded from quantitative synthesis.[37,38] Both are summarized narratively following SWiM guidance; neither consistently favored plasma. Comparability is limited by risk of bias and endpoint variation (Supplementary materials, Table A11).

Secondary outcomes

Across randomized and observational evidence, no clinically meaningful differences were identified between plasma and crystalloids for secondary outcomes. Rates of major adverse events – TRALI, TACO, venous/arterial thromboembolism, sepsis, multiorgan failure – were similar between groups.[22,23] On hospital arrival, hemostatic parameters (INR, lactate, hemoglobin) showed no relevant between-group differences. Twenty-four-hour transfusion endpoints – PRBC units transfused, massive transfusion activation, and CAT fulfillment – were not affected by plasma.[25,26] Hospital and ICU length of stay were comparable. Given endpoint heterogeneity, timing variation, and sparse events, quantitative pooling was not appropriate; instead, we used a structured, study-level synthesis (Table 4). Full details, including reasons for non-pooling, robustness checks, and GRADE ratings are provided in Supplementary Table A12. Overall, secondary outcomes do not support a clinical benefit of prehospital plasma over crystalloids.

Assessment of publication bias

In accordance with Cochrane and PRISMA 2020 guidance, publication bias was not formally assessed using funnel plots or tests for small-study effects because fewer than ten studies contributed to each outcome; below this threshold such analyses are considered unreliable and potentially misleading.[13] The Duval and Tweedie trim-and-fill method, prespecified as an exploratory sen-

Table 4. Secondary outcomes in the included studies.

Study (year, trial) [ref]	Hemostatic parameters (metric)	Adverse events	Transfusion requirements (24 h)	Resource use (LOS/ICU)	Overall direction	Risk of bias
Moore 2018 (COMBAT) [34]	INR, lactate, hemoglobin on arrival; median/IQR *(no conversions in table)*	Sepsis, MOF; TRALI/TACO rare or not reported	PRBC units within 24 h; MTP reported	Hospital LOS and ICU LOS; mean/SD	→ No clinically relevant difference	RoB 2: Some concerns
Sperry 2018 (PAMPer) [35]	Lactate on arrival/within 24 h; mixed formats	Sepsis, MOF; TRALI/TACO rare or not reported	PRBC within 24 h; MTP reported; local thresholds varied	Hospital LOS and ICU LOS; median/IQR	→ No clinically relevant difference	RoB 2: Some concerns
Jost 2022 (PREHO-PLYO) [36]	INR on arrival; median/IQR	Adverse events partly reported / not reported	PRBC within 24 h; median/IQR	Hospital LOS and ICU LOS; median/IQR	→ No clinically relevant difference	RoB 2: Some concerns
Henriksen 2016 [37]	In-hospital INR and lactate; heterogeneous metrics	Non-uniform complications	In-hospital transfusions, not standardized	Non-standardized hospital LOS	ND (not comparable with RCTs)	ROBINS-I: Serious
Shlaifer 2019 [38]	In-hospital Hb/INR, non-uniform	Non-uniform complications	In-hospital transfusions; non-uniform MT definitions	Non-uniform hospital/ICU LOS	ND (not comparable with RCTs)	ROBINS-I: Serious

Legend (abbreviations). Direction: ↑ favors plasma; ↓ favors crystalloids; → no clinically relevant difference; ND not determinable due to non-commensurability. MCIDs: PRBC ≥1 unit/24 h; INR ≥0.10; lactate ≥0.5 mmol/L; LOS ≥1 day. Median→mean/SD conversions, when used elsewhere, follow Wan et al.; not applied in this table (details in Supplement).

Table 5. Summary of Findings (SoF) using the GRADE approach.

Outcome	Population / comparison	Estimated effect	Studies (k) / N	Certainty (GRADE)	Main reasons for downgrading
24 hour mortality	Adults with major trauma; prehospital plasma vs crystalloids	OR 1.64 (0.56 to 4.82).[34]	1 RCT / 125	●●○○ Low	Imprecision (wide CI; optimal information size not met); k, 1 (inconsistency not assessable).[13]
28 to 30 day mortality	Same as above	OR 0.92 (0.49 to 1.72); prediction interval 0.35 to 2.43; I^2 50.6%.[34-36]	3 RCTs / 760	●●○○ Low	Risk of bias (two of three "some concerns"); imprecision (wide CI and prediction interval).
Major transfusion related adverse events (TRALI, TACO)	Same as above	No clear difference; not pooled.[34-36]	2 RCTs (partial reporting)	●○○○ Very low	Rare events; non uniform definitions; imprecision; possible misclassification.[22,23]
Hemostatic parameters on arrival (INR, lactate, hemoglobin)	Same as above	Trivial differences; not pooled.[34-38]	3 RCTs + 2 observational	●○○○ Very low	Heterogeneity of time points and metrics (median and IQR vs mean and SD); incomplete reporting.[13]
Transfusion requirements within 24 hours (PRBC, MT / MTP)	Same as above	No consistent reduction; not pooled.[34-38]	3 RCTs + 2 observational	●○○○ Very low	Non homogeneous definitions (MT / CAT / MTP); co interventions; risk of bias.[25,26]
Length of stay (hospital LOS / ICU LOS)	Same as above	No clinically relevant difference.[34-38]	3 RCTs (+ descriptive observational)	●○○○ Very low	Heterogeneous metrics; partial reporting; possible competing risk.

High, ●●●●, Moderate, ●●●○, Low, ●●○○, Very low, ●○○○. Legend (abbreviations). TRALI, transfusion related acute lung injury; TACO, transfusion associated circulatory overload; INR, international normalized ratio; PRBC, packed red blood cells; MT, massive transfusion; CAT, critical administration threshold; MTP, massive transfusion protocol; LOS, length of stay; ICU, intensive care unit; OIS, optimal information size; PI, prediction interval; RCT, randomized controlled trial; IQR, interquartile range; SD, standard deviation.

sitivity analysis for 28–30-day mortality, was not applied due to insufficient statistical power.[13]

Overall certainty of evidence (GRADE)

Based on GRADE, overall certainty for 28–30-day mortality was low, reflecting study-design limitations, small samples, and wide confidence intervals. Certainty for 24-hour mortality was also low due to reliance on a single imprecise trial. For secondary outcomes, certainty ranged from low to very low, primarily because of inconsistent outcome definitions, timing variability, and sparse events. These heterogeneities preclude confident conclusions about safety or hemostatic efficacy. While prehospital plasma remains biologically plausible, its clinical advantage over crystalloids is uncertain. Domain-level downgrading is summarized in Table 5.[24]

Discussion

Critical synthesis of findings and strength of evidence

This systematic review and meta-analysis, conducted in accordance with PRISMA 2020 and registered in PROSPERO (CRD420251027516), does not show any clinically or statistically significant benefit of prehospital plasma administration compared to standard crystalloid therapy in patients with hemorrhagic shock.[13] The quantitative synthesis of 28–30-day mortality, based on three major randomized trials, revealed an overall odds ratio of 0.92 (95% CI 0.49–1.72) with moderate heterogeneity (I^2 50.6%).[34-36] The limited precision of the findings, as reflected by wide and overlapping confidence intervals, appears to reflect operational variability rather than genuine therapeutic ineffectiveness. Specifically, discrepancies among the studies are mainly due to differences in the type of plasma administered, transport mode, treatment timing, and organization of prehospital care rather than intrinsic differences in clinical outcomes. Assessment of 24-hour mortality was not quantitatively feasible due to methodological heterogeneity and incomplete reporting; these data were therefore synthesized narratively,[34-36] underscoring the need for future studies with harmonized designs and shared endpoints. Secondary outcomes, including adverse events, coagulation parameters, and hemodynamic stability, were highly variable and lacked uniform definition, thus precluding meta-analytic synthesis. According to the GRADE framework, the overall quality of evidence is low for mortality outcomes and very low for secondary outcomes, mainly due to imprecision, inconsistency, and risk of bias.[24]

Clinical implications

Current evidence does not support a statistically or clinically significant survival benefit of prehospital plasma administration compared to standard crystalloid therapy, consistent with the latest European guidelines on major bleeding management in trauma.[8] However, targeted use may be considered in specific operational settings – such as prolonged transport times or suspected massive hemorrhage – where early plasma availability could facilitate damage-control resuscitation and early correction of trauma-induced coagulopathy. Potential benefit remains unproven and depends on multiple logistic and operational factors, including plasma type (fresh frozen *vs* lyophilized), thermal stability, reconstitution time, and the prehospital team's capacity to establish vascular access and promptly monitor transfusion reactions. In well-organized systems with short transport intervals and low hemorrhagic risk, the clinical impact of plasma appears minimal. Conversely, selective use in remote, austere, or military environments may be justified, provided adequate clinical oversight and supply chain robustness are ensured. Future evaluations should incorporate cost-effectiveness analyses, logistic sustainability, and transfusion governance.

Comparison with the international literature

Recent meta-analyses based on the three main randomized controlled trials (COMBAT, PAMPer, PREHO-PLYO; n=760) have yielded consistent findings, emphasizing the lack of a definitive survival advantage and confirming an acceptable safety profile of prehospital plasma administration.[11,39] However, both analyses relied on traditional random-effects models without adjustments for system-level variability or formal certainty of evidence assessments. This review was conducted to address these methodological limitations by incorporating a more robust statistical approach, implementing prior harmonization of outcome definitions, and systematically applying the GRADE framework. This enhances a more realistic estimation of effect dispersion and improves clinical transferability. The overall pooled estimate remains neutral (OR near unity with 95% confidence intervals encompassing both potential benefit and harm), confirming ongoing uncertainty about efficacy. Secondary outcomes do not demonstrate a consistent directional trend, while observational studies – downgraded for confounding – provide only qualitative support. A direct comparison of the three meta-analyses based exclusively on RCTs is presented in Supplementary materials, Table A13, demonstrating how methodological differences substantially influence interpretative judgments more than aggregate results. In conclusion, this review not only replicates but critically updates the existing evidence, providing a more coherent, precise, and clinically interpretable landscape of current uncertainty.

Strengths and limitations of the review

This review followed a preregistered protocol and rigorous methodological standards, with data extraction and risk-of-bias assessment independently performed by two reviewers. Major limitations, in addition to those previously discussed – such as protocol registration occurring after the literature search, a potential source of registration bias – include the lack of contact with primary study authors and limited generalizability to low-resource settings. Small-study effects and potential publication bias could not be rigorously assessed due to the small number of available studies. Moreover, restricting inclusion to studies published in English and Italian introduces potential language bias, reducing the completeness and generalizability of the evidence. Overall, these limitations underscore the need for future harmonized multicenter trials to overcome current evidence fragmentation and support more robust clinical decision-making

Implications for future research

Future research should prioritize pragmatic, multicenter trials with adequate power and rigorous designs to minimize bias. Individual randomization is preferable; for cluster trials, prespecify the Intracluster Correlation Coefficient (ICC), cluster size, and analytic corrections. Interventions should be standardized for plasma type, dose, timing, and protocol, with diligent documentation of logistics, cold-chain integrity, and protocol deviations. Primary outcomes should include 24- and 30-day mortality, alongside a harmonized set of clinical and safety endpoints with uniform definitions and timing. Maximum transparency requires preregistration in public registries and publication of the full protocol and sta-

tistical analysis plan before initiation. Studies should also assess cost-effectiveness, effects on transfusion services, and operational governance, and involve diverse geographic settings to enhance generalizability. Developing integrated clinical protocols and uniform prehospital pathways is a promising strategy to reduce outcome variability and improve clinical applicability.[40]

Conclusions

Available evidence does not demonstrate a survival benefit of prehospital plasma compared to crystalloids; secondary outcomes show no clinically relevant advantages, and the overall certainty of evidence remains low. Routine adoption is not indicated; selective use should be limited to structured EMS protocols with audit and safety monitoring. Before wider dissemination, harmonized multicenter trials with standardized outcomes and preregistered transparent methods are needed to produce robust and generalizable evidence

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Online supplementary materials
Table A1. Protocol version history (PRISMA item 24c).
Table A2. Full search strategies (PRISMA-S).
Table A3. PRESS checklist and reviewer feedback.
Table A4-1. Clinical and surrogate outcomes with clinical justification.
Table A4-2. Operational definitions of outcomes and clinical conditions used in the review.
Table A5. Analytic framework and model specifications used in the meta-analysis.
Table A6. Full-text reports assessed and excluded (PRISMA item 16).
Table A7. Traffic-light summary of risk of bias.
Table A8. Percent distribution of risk of bias by domain (n = 5 studies).
Table A9-1.Operational reasons for not pooling the 24-hour endpoint.
Table A9-2. Exploratory sensitivity (24-hour endpoint; k=2: COMBAT + PAMPer).
Table A10-1. Leave-one-out sensitivity for 28 to 30 day mortality (RCTs).
Table A10-2. Subgroup summaries for 28 to 30 day mortality (RCTs).
Table A11. Non-pooled comparative cohorts: context and reasons for exclusion from the meta-analysis.
Table A12. Secondary outcomes — synthesis, robustness, and certainty (SWiM/GRADE).
Table A13. Methodological comparison of the RCT-only meta-analyses on prehospital plasma.

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