Online supplementary materials

Table A1. Protocol version history (PRISMA item 24c)

Version	Date	Event / changes	Impact on the review
v1.0	12 April 2025	First registration in the International Prospective Register of Systematic Reviews (PROSPERO ID CRD420251027516).	None
v2.0	16 May 2025	Editorial clarifications (wording and descriptive details).	None (no changes to PICO, outcomes, or inclusion criteria)
v2.1	16 May 2025	Further editorial clarifications.	None (no changes to PICO, outcomes, or inclusion criteria)

Caption. Version history recorded for transparency in line with **PRISMA 2020** item **24c**. Registration occurred after the last search but before data extraction and analysis; all changes were editorial only

Table A2. Full search strategies (PRISMA-S)

Database (platform)	Full search string	Filters / limits	Last search date
PubMed / MEDLINE (NIH)	(("Wounds and Injuries"[MeSH] OR "Hemorrhage"[MeSH] OR trauma[tiab] OR haemorrhag*[tiab] OR hemorrhag*[tiab]) AND ("Emergency Medical Services"[MeSH] OR "Prehospital Care"[MeSH] OR prehospital*[tiab] OR "pre-hospital"[tiab] OR "out-of-hospital"[tiab] OR EMS[tiab]) AND ("Blood Plasma"[MeSH] OR "Plasma, Fresh Frozen"[MeSH] OR "fresh frozen plasma"[tiab] OR FFP[tiab] OR lyophiliz*[tiab] OR "freeze-dried"[tiab] OR FDP[tiab] OR "lyophilized plasma"[tiab]) AND ("Crystalloid Solutions"[MeSH] OR crystalloids[tiab] OR crystalloid*[tiab] OR saline[tiab] OR "normal saline"[tiab] OR "0.9% sodium chloride"[tiab] OR "lactated ringer*"[tiab] OR Hartmann*[tiab] OR "Plasma-Lyte"[tiab]))	Period: 2014-01-01 to 2025-04-15; Languages: English / Italian; no design filter	08 March 2025

Embase (Elsevier / Embase.com)	(('wound'/exp OR 'injury'/exp OR 'hemorrhage'/exp OR trauma:ti,ab OR haemorrhag*:ti,ab OR hemorrhag*:ti,ab) AND ('emergency medical service'/exp OR 'prehospital care'/exp OR prehospital*:ti,ab OR 'pre-hospital':ti,ab OR 'out-of-hospital':ti,ab OR EMS:ti,ab) AND ('blood plasma'/exp OR 'fresh frozen plasma'/exp OR 'fresh frozen plasma':ti,ab OR FFP:ti,ab OR lyophiliz*:ti,ab OR (freeze NEAR/3 dried):ti,ab OR FDP:ti,ab OR 'lyophilized plasma':ti,ab) AND ('crystalloid solution'/exp OR 'lactated ringer solution'/exp OR 'sodium chloride 0.9% solution'/exp OR crystalloid*:ti,ab OR 'lactated ringer*':ti,ab OR Hartmann*:ti,ab OR saline:ti,ab OR 'normal saline':ti,ab OR '0.9% sodium chloride':ti,ab OR 'Plasma-Lyte':ti,ab)) AND [2014-2025]/py	Period: 2014 to 2025; Languages: English / Italian; no design filter	08 March 2025
CINAHL (EBSCOhost)	((MH "Wounds and Injuries+" OR MH "Multiple Trauma" OR MH "Hemorrhagic Shock" OR TI trauma* OR AB trauma* OR TI injur* OR AB injur* OR TI "major trauma" OR AB "major trauma" OR TI polytrauma* OR AB polytrauma*) AND (MH "Prehospital Care+" OR MH "Emergency Medical Services+" OR TI prehospital* OR AB prehospital* OR TI "pre-hospital" OR AB "pre-hospital" OR TI "out-of-hospital" OR AB "out-of-hospital") AND (MH "Blood Plasma+" OR TI plasma* OR AB plasma* OR TI "fresh frozen plasma" OR AB "fresh frozen plasma" OR TI FFP OR AB FFP OR TI "lyophilized plasma" OR AB	Limiters: Publication date 2014-01-01 to 2025-04-15; Languages: English / Italian; no design filter	08 March 2025

	"lyophilized plasma" OR TI "freeze-dried plasma" OR AB "freeze-dried plasma" OR TI FDP OR AB FDP) AND (MH "Crystalloid Solutions+" OR TI crystalloid* OR AB crystalloid* OR TI saline OR AB saline OR TI "normal saline" OR AB "normal saline" OR TI "0.9% sodium chloride" OR AB "0.9% sodium chloride" OR TI "lactated ringer*" OR AB "lactated ringer*" OR ((TI Hartmann* OR AB Hartmann*) AND (TI (solution* OR infusion*) OR AB (solution* OR infusion*))) OR TI "compound sodium lactate" OR AB "compound sodium lactate" OR TI "Plasma-Lyte" OR AB "Plasma-Lyte"))		
Cochrane CENTRAL (Wiley / Cochrane Library)	(([mh "Wounds and Injuries"] OR [mh "Multiple Trauma"] OR [mh "Hemorrhagic Shock"] OR trauma*:ti,ab,kw OR injur*:ti,ab,kw OR "major trauma":ti,ab,kw OR polytrauma*:ti,ab,kw) AND ([mh "Prehospital Care"] OR prehospital*:ti,ab,kw OR "pre-hospital":ti,ab,kw OR "out-of-hospital":ti,ab,kw) AND ([mh "Blood Plasma"] OR plasma*:ti,ab,kw OR "fresh frozen plasma":ti,ab,kw OR FFP:ti,ab,kw OR "lyophilized plasma":ti,ab,kw OR "freeze-dried plasma":ti,ab,kw OR FDP:ti,ab,kw) AND ([mh "Crystalloid Solutions"] OR crystalloid*:ti,ab,kw OR saline:ti,ab,kw OR "0.9% sodium chloride":ti,ab,kw OR "lactated ringer*":ti,ab,kw OR Hartmann*:ti,ab,kw OR "Plasma-Lyte":ti,ab,kw))	Period: 2014 to 2025; no design filter	08 March 2025

Web of Science Core Collection (Clarivate)	TS=((trauma* OR injur* OR "major trauma" OR polytrauma* OR "hemorrhagic shock") AND (prehospital* OR "pre-hospital" OR "out-of-hospital") AND (plasma OR "fresh frozen plasma" OR FFP OR "lyophilized plasma" OR "freeze-dried plasma" OR FDP) AND (crystalloid* OR saline OR "0.9% sodium chloride" OR "lactated ringer*" OR Hartmann* OR "Plasma-Lyte"))	Timespan: 2014 to 2025; Languages: English OR Italian; no design filter	08 March 2025

Notes (search methods). High sensitivity PICO strategy combining controlled vocabulary (MeSH / Emtree / CINAHL Headings) and free text in title and abstract; truncation and proximity operators used where supported. No study design filters applied. Dates are formatted in English and ranges expressed with to.

Table A3. PRESS checklist and reviewer feedback

PRESS item	Outcome	Reviewer comments (summary)	Authors' response / action
Scope / focus (PICO, population, intervention, comparator, outcomes, context)	Adequate	Well defined question; avoid filtering by outcomes to preserve sensitivity.	No outcome filters applied in databases; outcomes used only to organise extraction.
Controlled vocabularies (MeSH / Emtree / Headings)	Needs improvement → Updated	Recommend exploding *Prehospital Care* and *Blood Plasma*; harmonise headings across databases.	Added explode where appropriate; harmonised terms across PubMed, Embase, CINAHL, and CENTRAL.
Free text / synonyms / variants	Needs improvement → Updated	Add variants: "pre hospital", "out of hospital"; for crystalloids include balanced crystalloids, Hartmann, Plasma Lyte; for plasma include freeze dried / lyophilized, FDP / LP.	Terms added to search strings (see Table A2).
Boolean logic and proximity	Adequate	Check nested parentheses; consider NEAR/x in Embase to link "blood product*" with "units / volume".	Parentheses verified; introduced NEAR/3 in Embase where useful.

Field tags / interface syntax	Needs improvement → Normalised	Standardise tags: [tiab] in PubMed; :ti,ab in Embase; TI/AB in CINAHL; specify ti,ab,kw in CENTRAL.	Syntax normalised and documented in Table A2.
Limits and filters (date / language / study type)	Adequate	Avoid design filters; justify language and time window limits.	No design filters; English / Italian and 2014 to 2025 limits justified by eligibility criteria.
Databases and platforms	Adequate	List database plus interface and last search date for each; indicate grey sources and registries.	Table A2 with databases, interfaces, dates; registries and grey sources documented.
Deduplication and traceability	Adequate	Specify software and matching rules; report pre and post deduplication counts.	Deduplication with EndNote X9 and screening in Rayyan; per source counts and duplicates removed reported

Notes. PRESS reviewer: **MS**, information retrieval specialist. The preliminary strategy was piloted on a sample by two reviewers (**RG, CL**).

Table A4-1. Clinical and surrogate outcomes with clinical justification

Category	Outcome	Type	Clinical justification
Primary	24-hour mortality	Clinical	Early endpoint to assess timeliness and effectiveness of hemostatic therapy.[20],[21]
Primary	30-day mortality	Clinical	Established endpoint capturing overall survival and late complications.[21]
Secondary — clinical	Major transfusion-related adverse events (TRALI, TACO), VTE/ATE, sepsis, MOF	Clinical	Safety outcomes reflecting the risk–benefit profile of hemostatic therapy.[22],[23]
Secondary — hospital	Hospital length of stay (LOS)	Hospital	Resource use; proxy of recovery trajectory.[21]
Secondary — hospital	ICU length of stay	Hospital	Critical-care resource use; severity proxy.[21]
Secondary — surrogate	Serum lactate	Surrogate	Marker of tissue perfusion; related to shock-induced hypoxia but less robust for survival.[21]
Secondary — surrogate	INR	Surrogate	Indicator of correction of trauma-induced coagulopathy.[21]
Secondary — surrogate	Hemoglobin (Hb)	Surrogate	Indirect measure of blood loss and/or resuscitation effectiveness.[21]
Secondary — surrogate	Platelet count	Surrogate	Component of the hemostatic profile at presentation.[21]

Secondary — transfusion	PRBC units within 24 hours	Transfusion	Quantifies early transfusion exposure and blood-component need; linked to hemorrhage severity.[21]
Secondary — transfusion	Massive transfusion (MT ≥10 units/24 h; CAT ≥3 units/1 h)	Transfusion	Severity markers; standard definition (MT) or operational threshold (CAT) in modern DCR protocols.[25–26]
Secondary — organizational	Massive transfusion protocol (MTP) activation	Organizational	Institutional response within DCR; associated with hemorrhage severity and transfusion burden.[7–8]

Legend (abbreviations). TRALI, transfusion-related acute lung injury; **TACO**, transfusion-associated circulatory overload; **VTE/ATE**, venous or arterial thromboembolism; **MOF**, multiple organ failure; **LOS**, length of stay; **ICU**, intensive care unit; **INR**, international normalized ratio; **Hb**, hemoglobin; **PRBC**, packed red blood cells; **MT**, massive transfusion; **CAT**, critical administration threshold; **MTP**, massive transfusion protocol; **DCR**, damage control resuscitation.

Table A4-2. Operational definitions of outcomes and clinical conditions used in the review

Term	Adopted definition
Massive transfusion (MT)	≥10 PRBC units within 24 hours; operational alternative CAT = ≥3 PRBC units within 1 hour.[25–26] Thresholds that differ (e.g., >4 units in 60 minutes) are not fully comparable with CAT and were used only in narrative synthesis or sensitivity analyses.[26]
Severe hemorrhagic shock	SBP <90 mm Hg with signs of hypoperfusion (e.g., lactate >4 mmol/L or altered mental status), consistent with ATLS guidance. *Note:* clinical frame; eligibility criteria remain SBP <90 and/or HR >120 or RTS ≤10.[9,19]
Trauma-induced coagulopathy (TIC)	INR >1.5 at first blood draw (on hospital arrival/shock room); criterion consistent with European bleeding-management guidelines (see also the updated clinical frame).[7,8,21]
Fresh frozen plasma (FFP)	Plasma derived from whole blood, frozen within 8 hours of collection and thawed immediately before infusion; specifications per AABB guidance.
Lyophilized plasma (LP)	Lyophilized plasma, room-temperature stable, reconstituted at the time of use; indicated for prehospital deployment (profile and logistics in out-of-hospital scenarios).[8]
Massive transfusion protocol (MTP)	Activation of the institutional MTP (hospital-specific criteria) within the DCR approach of European guidelines.[7–8]

Major transfusion-related adverse events	TRALI (2019 consensus update) and TACO (2019 international definition) treated as priority safety outcomes.[22],[23]

Legend (abbreviations). PRBC, packed red blood cells; **CAT**, critical administration threshold; **SBP**, systolic blood pressure; **HR**, heart rate; **RTS**, Revised Trauma Score; **ATLS**, Advanced Trauma Life Support; **INR**, international normalized ratio; **DCR**, damage control resuscitation; **TRALI**, transfusion-related acute lung injury; **TACO**, transfusion-associated circulatory overload.

Table A5. Analytic framework and model specifications used in the meta-analysis.

Analytic component	Description / method used	Reference / justification
Software	Stata v18.5	—
Model type	Random-effects (REML)	Cochrane Handbook[13]
Variance estimation	Hartung–Knapp–Sidik–Jonkman correction	Cochrane Handbook[13]
Effect measure	Odds ratio (log-transformed, back-transformed)	—
Heterogeneity metrics	Q, I^2, τ^2, and 95% prediction interval	Cochrane Handbook[13]
Cluster-RCT handling	Prioritized adjusted estimates; recalculated effective n when unavailable	Cochrane Handbook[13]
Zero-event handling	0.5 continuity correction for single-zero arms; double zeros excluded	Cochrane Handbook[13]
Continuous data	Not pooled due to heterogeneity in metrics (mean vs median, units)	—
Forest plot orientation	Values >1 favor survival; all results reported as OR for mortality	—
Subgroup analyses	Civilian vs military; FFP vs LP; ISS <25 vs ≥25 — per PROSPERO framework	PROSPERO CRD420251027516
Sensitivity analyses	Excluding high/critical-risk studies; military-only studies; restricting to 30-day endpoints	PROSPERO CRD420251027516

Meta-regression	Univariable: patient age, head injury, prehospital time	Cochrane Handbook[13]

Table A6. Full-text reports assessed and excluded (PRISMA item 16)

	Full citation (title and authors)	Primary PRISMA reason for exclusion
1	Reynolds PS, et al. Prehospital use of plasma for traumatic hemorrhage (PUPTH): study protocol for a randomized controlled trial. Trials. 2015;16:321. doi:10.1186/s13063-015-0844-5	Primary outcome (mortality) not reported
2	Sunde GA, Heltne JK, Lockey D, et al. Prehospital transfusion of plasma and red blood cells in air medical trauma transport. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S26–30. doi:10.1097/TA.0000000000000658	Irrelevant intervention / comparator
3	Glassberg E, et al. Point-of-injury use of reconstituted freeze-dried plasma as a resuscitative fluid: a special report for prehospital trauma care. J Trauma Acute Care Surg. 2013;75(2 Suppl 2):S95–S97. doi:10.1097/TA.0b013e31829d94c7	Ineligible population / context
4	Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of prehospital blood product transfusion during medical evacuation of combat injuries with survival. JAMA. 2017;318(16):1581–91. doi:10.1001/jama.2017.15097	Irrelevant intervention / comparator

5	Radwan ZA, Bai Y, Matinez L, et al. An emergency department thawed plasma protocol is associated with decreased blood component use and improved survival in trauma. JAMA Surg. 2013;148(2):170–5. doi:10.1001/jamasurg.2013.2676	Ineligible population / context
6	Reitz KM, Moore EE, Pusateri AE, et al. A combined analysis of the COMBAT and PAMPer trials of prehospital plasma resuscitation in trauma. J Trauma Acute Care Surg. 2020;89(5):815–23. doi:10.1097/TA.0000000000002736	Duplicate population / report
7	Gruen DS, et al. Association of prehospital plasma with survival in patients with traumatic brain injury: a secondary analysis of the PAMPer trial. JAMA Netw Open. 2020;3(1):e1918731. doi:10.1001/jamanetworkopen.2019.18731	Primary outcome (mortality) not reported
8	Canton SP, et al. Lactate as a mediator of prehospital plasma mortality reduction in hemorrhagic shock. J Trauma Acute Care Surg. 2021;91(4):637–44. doi:10.1097/TA.0000000000003206	Irrelevant intervention / comparator
9	Holcomb JB, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma (PROPPR trial). JAMA. 2015;313(5):471–82. doi:10.1001/jama.2015.12	Ineligible population / context
10	Holcomb JB, et al. Multicenter observational prehospital resuscitation on helicopter study. J Trauma Acute Care Surg. 2017;82(3):E1–E9. doi:10.1097/TA.0000000000001335	Ineligible population / context

11	Moore EE, et al. Plasma-first resuscitation to treat hemorrhagic shock during emergency ground transportation in an urban area: a preliminary report. Shock. 2014;41(Suppl 1):35–9. doi:10.1097/SHK.0000000000000110	Ineligible population / context
12	Moore HB, et al. Shock-induced systemic hyperfibrinolysis is attenuated by plasma-first resuscitation. J Trauma Acute Care Surg. 2015;79(6):897–904. doi:10.1097/TA.0000000000000858	Ineligible population / context
13	COMBAT Study Group. COMBAT trial: randomized trial of prehospital plasma for traumatic hemorrhage. JAMA. 2015. doi:10.1001/jama.2015.15174	Primary outcome time point not aligned with our primary endpoint

Table A7. Traffic-light summary of risk of bias

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

Legend (colour codes). 🟩 Low risk; 🟨 Some concerns / Moderate risk; 🟥 Serious / High risk.

† **D1** differs by design: randomization process for RoB 2 trials; confounding for ROBINS I observational studies.

Table A8. Percent distribution of risk of bias by domain (n = 5 studies)

Domain	Low (n, %)	Some concerns (n, %)	High / Serious (n, %)	Critical (n, %)
D1: Randomization / Confounding	1 (20.0%)	2 (40.0%)	2 (40.0%)	0 (0.0%)
D2: Deviations from intended interventions	**0 (0.0%)**	**5 (100.0%)**	0 (0.0%)	0 (0.0%)
D3: Missing outcome data	5 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
D4: Measurement of the outcome	3 (60.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)
D5: Selection of the reported result	3 (60.0%)	1 (20.0%)	1 (20.0%)	0 (0.0%)

Table A9-1.Operational reasons for not pooling the 24-hour endpoint**.**

Study (year, trial)	Design	24-h endpoint status	Reporting format	Denominator	Time-zero	Cluster adjustment required	Eligible for 24-h pooling	Reason codes
COMBAT (2018)[34]	Individually randomised (ground EMS)	Prespecified / analysed	Per-arm counts 8/65 vs 6/60; OR 1.23 (95% CI 0.45–3.34)	ITT	Explicit (prehospital randomisation)	No	No	A
PAMPer (2018)[35]	Cluster RCT (air EMS)	Secondary endpoint	Per-arm percentages 13.9% vs 22.1%	ITT (cluster)	Not harmonised with COMBAT	Yes	No	A, C
PREHO-PLYO (2022)[36]	Individually randomised (physician-staffed ground EMS)	Descriptive; not prespecified	Descriptive counts (“Within 24 h” 6/66 vs 9/68)	Not clearly ITT for 24 h	Not explicit	No	No	A, B

Legend (abbreviations). Operational commensurability of the 24-hour mortality endpoint across trials. A = non-uniform/unclear time-zero (immortal-time risk ≤24 h); B = non-standardised endpoint/denominators (descriptive, not prespecified); C = cluster design (requires cluster-adjusted estimates/variances). The 24-hour endpoint was not pooled; the primary meta-analysis focuses on 28–30-day mortality (k=3).

Table A9-2. Exploratory sensitivity (24-hour endpoint; k=2: COMBAT + PAMPer)

Study (year)	24-h deaths (plasma)	Total (plasma)	24-h deaths (control)	Total (control)	RR (24 h)	log-RR	SE(log-RR)	Weight %	Notes
COMBAT (2018)[34]	8	65	6	60	1.23	0.2070	0.5096	—	Individually randomised
PAMPer (2018)[35]	—	ITT (cluster)	—	ITT (cluster)	RR (cluster-adjusted) = [insert]	*[calc]*	[from cluster model or design-effect]	—	Cluster RCT; per-arm % 13.9% vs 22.1%
Pooled (REML–HKSJ)					not calculated (cluster-adjusted variance pending)			I^2 / τ^2	Exploratory; does not alter the 28–30-day inference

Caption. Exploratory 24-hour sensitivity using *log-risk ratios* and *REML with Hartung–Knapp***.** *PAMPer* must be entered with a cluster-adjusted estimate/variance (or variance corrected via a documented design effect/ICC*).* PREHO-PLYO excluded (non-standardised 24-h endpoint). Report $\boldsymbol{I^2}$ and $\boldsymbol{\tau^2}$ only after the PAMPer variance is provided. Current qualitative pattern does ***not*** change the primary 28–30-day inference.

Table A10-1. Leave-one-out sensitivity for 28 to 30 day mortality (RCTs)

Configuration	k	OR for mortality (95% CI)	I^2
Pooled (all RCTs: COMBAT, PAMPer, PREHO-PLYO)	3	0.92 (0.49 to 1.72)	50.6%
Excluding COMBAT (Moore 2018)	2	0.84 (0.45 to 1.57)	46%
Excluding PAMPer (Sperry 2018)	2	1.15 (0.64 to 2.06)	0%
Excluding PREHO-PLYO (Jost 2022)	2	0.71 (0.33 to 1.53)	0%

Model: random effects (REML) with HKSJ correction. **Direction:** OR < 1.00 favours plasma.

Table A10-2. Subgroup summaries for 28 to 30 day mortality (RCTs)

Subgroup factor (prespecified)	Levels contrasted	Contributing trials (k)	Direction of effect	Notes (why no interaction test / pooling limits)
Transport mode	Air EMS vs Ground EMS	PAMPer[35] (k = 1) vs COMBAT[34] + PREHO-PLYO[36] (k = 2)	Air EMS: signal toward benefit (PAMPer). Ground EMS: neutral or not favourable overall.	Only one air trial; ground trials heterogeneous; k too small for a reliable subgroup test.
Plasma product	FFP / FP24 vs LP (lyophilized)	COMBAT[34] + PAMPer[35] (k = 2) vs PREHO-PLYO[36] (k = 1)	FFP / FP24: mixed (one favourable, one not). LP: neutral (single RCT).	LP informed by a single study; across-product comparison underpowered (no test of interaction).
Clinical severity	ISS < 25 vs ISS ≥ 25	Not consistently reported	—	ISS subgroup data not available across trials; no pooling possible.

Setting	Civilian vs Military	All RCTs civilian (k = 3): COMBAT[34], PAMPer[35], PREHO-PLYO[36]	—	No military RCT; military evidence is observational only (see Appendix A, Table A10).
Time to evacuation	Short vs Prolonged	Narrative contrast: ~20–30 min (COMBAT[34], PREHO-PLYO[36]) vs ~40–50 min (PAMPer[35])	Longer evacuation associated with the trial showing benefit.	Heterogeneous definitions and no patient-level times; hypothesis-generating only.
Design	Cluster RCT vs Individual RCT	PAMPer[35] (cluster) vs COMBAT[34] + PREHO-PLYO[36] (individual)	Cluster trial favourable; individual trials neutral or not favourable.	Single cluster trial; design alone cannot explain differences.

Table A11. Non-pooled comparative cohorts: context and reasons for exclusion from the meta-analysis

Study (year)	Design / setting	Plasma type	Reported mortality outcome	Time point vs 24 h / 28–30 d	Comparator	Primary reason for exclusion from pooling	Risk of bias	Impact on this review
Henriksen — 2016[37]	Prospective civilian cohort	Prehospital FFP (often with other blood components)	In-hospital mortality	Not aligned (no 24 h or 28–30 d data)	Standard care without prehospital plasma	Time point not mappable to primary endpoints; heterogeneous definitions and co-interventions	ROBINS I: Serious (residual confounding, selection)	Narrative synthesis only (SWiM); did not contribute to pooling
Shlaifer — 2019[38]	Retrospective military cohort (Israel)	LP (lyophilized plasma)	In-hospital mortality	Not aligned (no 24 h or 28–30 d data)	No prehospital plasma	Time point not mappable; military setting with non uniform co-interventions	ROBINS I: Serious (incomplete matching, post hoc analyses)	Narrative synthesis only (SWiM); excluded from pooling

Legend (abbreviations). FFP = fresh frozen plasma; FP24 = plasma frozen within 24 hours; LP = lyophilized plasma; SWiM = Synthesis Without Meta-analysis; ROBINS I = Risk Of Bias In Non-randomized Studies of Interventions.

Table A12. Secondary outcomes — synthesis, robustness, and certainty (SWiM/GRADE)

Outcome (definition)	Pooled?	Effect (metric)	I^2 / τ^2	95% PI	Leave-one-out (robustness / driver)	Reason for no pooling / SWiM rule	GRADE (reason)
PRBC within 24 h (units)	No	—	—	—	Direction signal driven by PAMPer; quantitative LOO N/A (no pooling)	Non-commensurable formats (median vs mean; site-specific MTP/CAT thresholds).	Very low — imprecision, inconsistency, measurement heterogeneity
INR on arrival	No	—	—	—	Direction signal PAMPer-dependent; LOO N/A	Heterogeneous reporting; unit/scale handling inconsistent across trials.	Very low — imprecision, incomplete reporting, risk of misclassification
Lactate (arrival / 24 h)	No	—	—	—	No consistent direction; LOO N/A	Non-aligned time points; units not uniform.	Very low — imprecision, heterogeneity of timing/metrics

TRALI	No	—	—	—	Rare events; LOO N/A	Event rarity; varying surveillance/definitions across studies	Very low — rarity, possible misclassification
TACO	No	—	—	—	Rare events; LOO N/A	Event rarity; non-uniform case definitions	Very low — rarity, misclassification risk
Venous/arterial thrombosis	No	—	—	—	No coherent direction; LOO N/A	Sparse events; ascertainment differences	Very low — imprecision, detection heterogeneity
Sepsis	No	—	—	—	No coherent direction; LOO N/A	Variable diagnostic criteria and timing	Very low — imprecision, non-uniform definitions
MOF (multi-organ failure)	No	—	—	—	No coherent direction; LOO N/A	Non-standard outcome definitions; competing risks	Very low — imprecision, outcome heterogeneity
Hospital LOS (days)	No	—	—	—	No coherent direction; LOO N/A	Median vs mean; skewness; discharge practices differ.	Very low — imprecision, competing risk bias
ICU LOS (days)	No	—	—	—	No coherent direction; LOO N/A	As above (LOS).	Very low — imprecision, heterogeneity

MTP activation (yes/no)	No	—	—	—	No coherent direction; LOO N/A	Different local triggers/thresholds (non-commensurable)	Very low — inconsistency, indirectness
CAT fulfilment (≥3 PRBC/1 h)	No	—	—	—	No coherent direction; LOO N/A	CAT reported variably or absent; thresholds differ	Very low — imprecision, inconsistency

Legend (abbreviations). CAT = critical administration threshold; ICU = intensive care unit; INR = international normalized ratio; LOS = length of stay; MCID = minimal clinically important difference; MOF = multi-organ failure; MTP = massive transfusion protocol; PRBC = packed red blood cells; SWiM = Synthesis Without Meta-analysis; TRALI = transfusion-related acute lung injury; TACO = transfusion-associated circulatory overload.

SWiM rules (pre-specified).

Direction of effect coded as: ↑ favors plasma; ↓ favors crystalloids; → no clinically relevant difference.

No pooling when time points, metrics, or definitions are non-commensurable or when k is insufficient for reliable HKSJ inference.

Median→mean/SD conversions (when used elsewhere) follow Wan et al. [28] and are documented in the Supplement**.**

Table A13. Methodological comparison of the RCT-only meta-analyses on prehospital plasma

Item	Abuelazm 2024[39]	AlJoaib 2024[11]	Present review (RCT-only)
Evidence set	3 RCT (COMBAT, PAMPer, PREHO-PLYO)	3 RCT (same)	3 RCT (same)
Total N (RCT)	760	760	760
Effect measure (dichot.)	RR	RR	OR (mortality)
Model / estimator	Random-effects (DerSimonian–Laird)	Random-effects (DerSimonian–Laird)	Random-effects (REML) + HKSJ
Software	RevMan	RevMan	Stata 18.5
Heterogeneity reported	I^2 (τ^2 not explicit)	I^2 (qualitative thresholds)	I^2 50.6%; τ^2 0.16
Prediction interval	Not reported	Not reported	95% PI 0.35–2.43
Cluster-RCT handling	Standard (not detailed)	Standard	Cluster-adjusted estimates prioritised; design-effect if needed

Zero-event handling	RevMan defaults	RevMan defaults	Additive continuity correction 0.5; double-zero excluded
Time-point alignment	24 h; 28–30 d	24 h; 28–30 d	Pre-specified 28–30 d; sensitivity = exact 30 d
Sensitivity / robustness	Standard exclusions	Standard	Leave-one-out; exclusion of high/critical RoB
Secondary outcomes	Signal: ↓PRBC (−0.83), ↑INR (+0.07); no PI; robustness NA	No consistent benefit (MOF/ALI/vasopressors)	Pooling only if commensurable; SWiM + MCID; leave-one-out identifies trial drivers
GRADE	Reported (summary)	Reported (summary)	Outcome-level; Low for mortality (imprecision + inconsistency)
Bottom line	No mortality benefit; secondary signals uncertain	No mortality benefit; safety favourable	No mortality benefit; dispersion quantified (PI); secondary effects not robust/clinically irrelevant

Legend (abbreviations). ALI, acute lung injury; HKSJ, Hartung–Knapp–Sidik–Jonkman; PI, prediction interval; PRBC, packed red blood cells; REML, restricted maximum likelihood; RCT, randomized controlled trial; RoB, risk of bias; RR, risk ratio; SWiM, Synthesis Without Meta-analysis.