Raccomandazioni 23-24 della Linea Guida per la gestione integrata del trauma maggiore dalla scena dell'evento alla cura definitiva

Questo documento rappresenta la versione finale delle raccomandazioni cliniche che hanno completato l'intero processo previsto dal Manuale metodologico per la produzione di linee guida dell'Istituto Superiore di Sanità, inclusa la consultazione pubblica e la revisione esterna indipendente.

Il documento finale della presente Linea Guida sarà pubblicato quando il processo di elaborazione di tutte le raccomandazioni relative ai quesiti clinici sarà ultimato.

Luglio 2021

INDICE

Premessa

Il quesito clinico cui il panel risponde con le raccomandazioni n. 23 e n. 24 si riferisce al recupero volemico nel traumatizzato a seguito di shock emorragico. Questo trattamento prevede una continuità delle cure dalla fase pre-ospedaliera all'intra-ospedaliera, senza che vi sia la possibilità nelle diverse fasi del processo di differenziare le evidenze scientifiche, in particolare quelle inerenti all'utilizzo degli emocomponenti. Pertanto, parte delle valutazioni presentate in questa LG saranno utilizzate anche per formulare le raccomandazioni inerenti le modalità di gestione di un protocollo di trasfusione massiva, che normalmente si inizia una volta che il paziente è stato ammesso al dipartimento d'urgenza.

Lista delle raccomandazioni formulate

Quesito 12: Qual è il miglior fluido per l'espansione volemica da utilizzare nella rianimazione in corso di shock emorragico?

Raccomandazione 23. Nel paziente traumatizzato con emorragia si raccomanda in sede pre-ospedaliera l'utilizzo dei cristalloidi per il recupero della volemia, se gli emocomponenti non sono disponibili [Raccomandazione forte, qualità delle prove bassa].

Raccomandazione 22. Nel paziente traumatizzato con emorragia in sede pre-ospedaliera, quando possibile, considerare la trasfusione di emocomponenti [Raccomandazione condizionata, qualità delle prove bassa].

Il panel di esperti ha formulato le due raccomandazioni draft seguendo un processo metodologicamente rigoroso che, in conformità a quanto previsto dal Manuale metodologico dell'ISS, ha utilizzato il GRADE Evidence to Decision (EtD) framework per procedere in modo strutturato e trasparente dalle prove alla raccomandazione.

La valutazione degli interessi dichiarati dai membri del panel non ha rilevato nessun potenziale o rilevante conflitto di interesse rispetto alla tematica oggetto del quesito clinico.

Di seguito si riportano l'**EtD framework** e le appendici per le raccomandazioni 23 e 24:

- Appendice A – Quesito clinico e Strategia di ricerca
- Appendice B – Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione
- Appendice C – Sintesi delle evidenze
- Appendice D – Valutazione della qualità metodologica degli studi inclusi
- Appendice E – Tabelle delle evidenze
- Appendice F – Bibliografia degli studi inclusi
- Appendice G – Costi e valutazioni economiche
- Appendice H – Accettabilità e Fattibilità
- Appendice I – Bibliografia degli studi inclusi.

Per i dettagli su: Gruppo di sviluppo della LG, Policy per la gestione del Conflitto di Interesse (CdI), Scope e Metodologia fare riferimento al documento **LGTM_Racc1_4_def** scaricabile dal link: https://www.iss.it/documents/20126/8404212/LGTM_Racc1_4_def.

EtD framework – Quesito clinico n. 12

Qual è il miglior fluido per l'espansione volemica da utilizzare nella rianimazione in corso di shock emorragico?	
POPOLAZIONE:	Bambini, giovani e adulti con emorragia acuta a seguito di un incidente traumatico. Esclusi: Persone con un trauma maggiore derivante da ustioni. Pazienti in stato di shock non dovuto a trauma.
INTERVENTO:	Globuli rossi Plasma fresco congelato Plasma liquido Cristalloidi Plasma liofilizzato Sangue intero zero negativo a basso titolo
CONFRONTO:	Un confronto o una combinazione di quanto sopra (compresi diversi rapporti)
ESITI PRINCIPALI:	**Critici** Mortalità a 24 ore, 30 giorni / 1 mese e 12 mesi. Qualità della vita. Durata della degenza in terapia intensive Eventi avversi Reazione trasfusionale acuta: • Reazione emolitica alla trasfusione - acuta • Reazione trasfusionale emolitica - ritardata • Porpora post-trasfusionale • Complicanze trasfusionali precedentemente non categorizzate • Graft versus host disease associata a trasfusione • Sovraccarico circolatorio associato a trasfusione • Dispnea associata a trasfusione • Danno polmonare acuto correlato alla trasfusione • Infezioni trasmesse attraverso le trasfusioni. **Importanti** Time to definitive control of haemorrhage Patient-reported outcomes: return to normal activities psychological wellbeing) Tempo per il controllo definitivo dell'emorragia ***(correzione coagulopatia)***. Risultati riferiti dai pazienti: ritorno alle normali attività benessere psicologico) Dimensione della popolazione e trasferibilità: • nessuna limitazione sulla dimensione del campione non saranno presi in considerazione studi condotti su popolazioni indirette (diverse dalla popolazione oggetto del quesito).
SETTING:	Pre-ospedaliero (incluso il militare).
PROSPETTIVA:	Popolazione, SSN: • organizzazione ed erogazione de servizi per la gestione dei pazienti con trauma; • rete regionale per il trauma;

	• personale sanitario dei servizi di emergenza territoriale.
CONFLITTI DI INTERESSE	La policy ISS relativa alla dichiarazione e gestione del conflitto di interessi è stata applicata e non è stato identificato nessun interesse rilevante o potenzialmente rilevante. Tutti i membri del panel presenti alla riunione hanno votato, determinando la direzione e la forza della raccomandazione.

VALUTAZIONE

Problema

Il problema è una priorità?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ○ Probabilmente si ● Si ○ Varia ○ Non so	Il 40% dei decessi da trauma maggiore è imputabile ad un'emorragia non controllata, che rimane la principale causa di morte prevenibile (Kauvar, Lefering et al. 2006, Alexandrescu, O'Brien et al. 2009). L'emorragia non controllata richiede una rapida identificazione ed un'azione immediata finalizzata al ripristino della volemia per il mantenimento della perfusione degli organi ed in particolare del tessuto cerebrale, mentre si attua il controllo temporaneo o definitivo del focolaio emorragico. L'espansione volemica con fluidi è il primo step nella gestione emodinamica del paziente con shock emorragico: la rapida stabilizzazione del sistema cardiovascolare può proteggere il paziente da conseguenze severe da shock ipovolemico (Cannon 2018). Non c'è ancora consenso su quali fluidi dovrebbero essere usati nei pazienti traumatizzati. **Problema della coagulopatia** La somministrazione di fluidi nel paziente traumatizzato con emorragia, senza l'aggiunta di emocomponenti/emoderivati, determina una progressiva diluizione del sangue con calo della concentrazione di emoglobina (quindi della capacità di trasporto dell'Ossigeno) e dei fattori della coagulazione (Poole, 2016). Pertanto, è indispensabile iniziare al più presto la somministrazione di emoderivati/emocomponenti con la duplice finalità di mantenere il trasporto di Ossigeno e prevenire l'insorgenza della coagulopatia diluizionale con le possibili conseguenze sull'emostasi.	

Effetti desiderabili

Quanto considerevoli sono gli effetti desiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Irrilevanti ○ Piccoli ○ Moderati ● Grandi ○ Variano ○ Non so	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati identificati 29 records dall'aggiornamento della strategia di ricerca e 3 records (2 RCTs e 1 studio osservazionale) sono stati recuperati dalla LG NICE NG39. In totale, sono state incluse 14 revisioni sistematiche, 7 studi randomizzati e controllati e 11 studi osservazionali. Sono state identificate 4 domande cliniche maggiori con relative sotto domande: • Comparison 1. Crystalloids -**Appendice C1** 1. hypertonic saline/dextran or hypertonic saline versus isotonic fluid 2. normal saline versus lactated ringer's solution	L'utilizzo di emcomponenti, in particolare dei globuli rossi, anche nel pre-ospedaliero, è una modalità terapeutica già adottata in ambito civile a livello internazionale ed è considerata la strategia per ridurre la "blood failure"(debito di ossigeno associato al danno endoteliale causa della coagulopatia da trauma.

	3. plasmalyte A versus normal saline (inclusi: 1 RS, 1 RCT, 1 osservazionale) • Comparison 2. Blood components vs standard care -**Appendice C2** 1. prbcs versus standard care 2. prbcs + plasma versus standard care 3. plasma versus standard care 4. prbcs + cryoprecipitate verus no cryoprecipitate 5. high c:prbc versus low c:prbc (inclusi: 2 RS, 5 RCTs in awaiting assessment, 3 osservazionale) • Comparison 3. Blood components ratio -**Appendice C3** 1. FFP:PLT:PRBC 2. FFP:PRBC 3. PLT:PRBC (inclusi: 7 RS, 1 RCT, 6 osservazionale) • Comparison 4. Whole blood vs component therapy -**Appendice C4** (inclusi: 6 RS, 1 RCT, 1 osservazionale) La descrizione delle prove di evidenza si rimanda alle appendici C indicate nelle singole comparazioni.	(*Bjerkvig CK et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion 2016; 56;S182–S189*)
Effetti indesiderabili Quanto considerevoli sono gli effetti indesiderabili attesi?		
GIUDIZI	**RICERCA DELLE PROVE**	**CONSIDERAZIONI AGGIUNTIVE**
○ Grandi ● Moderati ○ Piccoli ○ Irrilevanti ○ Variano ○ Non so	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati identificati 29 records dall'aggiornamento della strategia di ricerca e 3 records (2 RCTs e 1 studio osservazionale) sono stati recuperati dalla LG NICE NG39. In totale, sono state incluse 14 revisioni sistematiche, 7 studi randomizzati e controllati e 11 studi osservazionali. Sono state identificate 4 domande cliniche maggiori con relative sotto domande: • Comparison 1. Crystalloids -**Appendice C1** 1. hypertonic saline/dextran or hypertonic saline versus isotonic fluid 2. normal saline versus lactated ringer's solution 3. plasmalyte A versus normali saline (inclusi: 1 RS, 1 RCT, 1 osservazionale) • Comparison 2. Blood components vs standard care -**Appendice C2**	In considerazione della severità degli eventi attesi e della loro frequenza e dell'under-reporting bias negli studi considerati, il panel si è orientato verso "Moderati".

	1. prbcs versus standard care 2. prbcs + plasma versus standard care 3. plasma versus standard care 4. prbcs + cryoprecipitate verus no cryoprecipitate 5. high c:prbc versus low c:prbc (inclusi: 2 RS, 3 osservazionale) • Comparison 3. Blood components ratio -**Appendice C3** 1. FFP:PLT:PRBC 2. FFP:PRBC 3. PLT:PRBC (inclusi: 7 RS, 1 RCT, 6 osservazionale) • Comparison 4. Whole blood vs component therapy -**Appendice C4** (inclusi: 6 RS, 1 RCT, 1 osservazionale) Per la a descrizione delle prove di evidenza si rimanda alle appendici C indicati nelle singole comparazioni.	

Qualità delle prove

Qual è la qualità complessiva delle prove di efficacia e sicurezza?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Molto bassa ● Bassa ○ Moderata ○ Alta ○ Nessuno studio incluso	Il rischio di bias degli studi valutati è in **Appendice D;** mentre la qualità delle prove complessivamente è molto eterogenea negli outcome considerati dalle revisioni sistematiche e dagli studi primari inclusi. Di seguito si riporta una valutazione globale mentre le singole Summary of Findings con giudizio GRADE sono in **Appendice E:** • **Comparison 1.** Crystalloids -Appendice E1: **da bassa ad alta** • **Comparison 2.** Blood components vs standard care -Appendice E2: **da molto bassa a moderata** • **Comparison 3.** Blood components ratio -Appendice E3: **da molto bassa a bassa** • **Comparison 4.** Whole blood vs component therapy -Appendice E4: **molto bassa**.	È stato dato particolare rilievo ai risultati sulla mortalità e al RoB relativo. **In merito all'utilizzo del concentrato di fibrinogeno, pur mancando studi che ne dimostrino il beneficio clinico in ambito preospedaliero, esso può avere un impiego per evitare il peggioramento della coagulopatia (RCT prehospital Clean THC study group Eur J Anaesth 2021, 38, 348-357), con outcome surrogato su controllo della coagulopatia**).

	MORTALITY	HEALTH RELATED QUALITY OF LIFE	LENGTH OF INTENSIVE CARE STAY	ADVERSE EFFECTS	ACUTE TRANSFUSION REACTION	TIME TO CONTROL HEMORRAGE	PATIENT REPORTED OUTCOME
COMPARAZIONE 1							
HYPERTONIC SALINE/DEXTRAN OR HYPERTONIC SALINE VERSUS ISOTONIC FLUID	1 RS Survival 24h: **HIGH** 1 RS Survival to hospital discharge rate : **MODERATE** 1 RS Survival at 30 days: **MODERATE** 1 RS Overall mortality: **MODERATE**		1 RS: **MODERATE**				
NORMAL SALINE VERSUS LACTATED RINGER'S SOLUTION PLASMA LYTE A VERSUS NORMALI SALINE	1 osservazionale Mortality at 30 days: **LOW** 1 RCT Mortality at 30 days: **LOW**						
COMPARAZIONE 2							
PRBCS VERSUS STANDARD CARE	at 24 hours: **VERY LOW** at 30 days: **VERY LOW**			Under estimation	**VERY LOW**		
PRBCS + PLASMA VERSUS STANDARD CARE	at 24 hours: **VERY LOW** at 30 days: RCT:**MODERATE** OSSERVAZIONALI:**LOW**		1 RCT: **MODERATE**	1 RCT: **MODERATE**	1 RCT: **MODERATE** 1 RS (RCT +OSSERVAZIONALI): **VERY LOW**		
PLASMA VERSUS STANDARD CARE	at 24 hours: Rijnhout 2019 SR (1 RCT): **MODERATE** Coccolini 2019 SR (2 RCT): **HIGH** at 30 days: Rijnhout 2019 SR (1 RCT): **MODERATE** Coccolini 2019 SR (2 RCT): **MODERATE**		1 RCT: **MODERATE**	1 RCT: **MODERATE**	1 RCT: **MODERATE**		
PRBCS + CRYOPRECIPITATE VERUS NO CRYOPRECIPITATE	at 24 hours- 1 osservazionale: **VERY LOW** Mortality in-hospital-1 osservazionale: **VERY LOW**			1 osservazionale: **VERY LOW**			
HIGH C:PRBC VERSUS LOW C:PRBC	1 multicenter prospective cohort study: **VERY LOW**			1 cohort study: **VERY LOW**			
COMPARAZIONE 3							
FFP PLT PRBC	From **LOW** to **VERY LOW**						
FFP:PRBC RATIO	3 RS: **LOW**			2 RS: **LOW**		Pediatric population	

	PLT:PRBC	Pediatric population (2osservazionali), Mortality at 24 hours: **LOW**					(1 osservazionale): **LOW**
	COMPARAZIONE 4						
	WHOLE BLOOD VS COMPONENT THERAPY	at 24 hours: **VERY LOW** at 30 days: **VERY LOW**	1 OSSERVAZIONALE: **VERY LOW**	1 RCT: **VERY LOW**	1 RCT: **VERY LOW** 1 RCT: **VERY LOW**	1 RCT: **VERY LOW** 1 RCT: **VERY LOW**	1 OSSERVAZIONALE: **VERY LOW**

Valori

C'è incertezza o variabilità nel valore attribuito agli esiti principali?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Importante incertezza o variabilità ● Possibile importante incertezza o variabilità ○ Probabilmente nessuna incertezza o variabilità importante ○ Nessuna incertezza o variabilità importante	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 28 records. Nessuno studio incluso.	L'incertezza attribuita al valore degli esiti è legata alle eventuali problematiche inerenti le disposizioni anticipate o le credenze religiose.

Bilancio degli effetti

Il bilancio tra effetti desiderabili ed indesiderabili favorisce l'intervento o il confronto?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ È in favore del confronto ○ Probabilmente è in favore del confronto ○ Non è in favore né dell'intervento né del confronto ● Probabilmente è in favore dell'intervento ○ È in favore dell'intervento ○ Varia ○ Non lo so	Le prove sono limitate.	Globalmente a favore dell'outcome critico più importante (mortalità), con basso livello di qualità delle prove, per emocomponenti ed emoderivati.

Risorse necessarie

Qual è l'entità delle risorse necessarie (costi)?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Costi elevati ● Costi moderati ○ Costi e risparmi irrilevanti ○ Risparmi moderati ○ Risparmi elevati ○ Varia ○ Non so	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati reperiti 40 articoli ed inclusi 8 studi. (**vedi appendice F**) Esistono molte fonti per stimare i costi delle diverse unità di plasma. non è possibile considerare evidenze internazionali dal momento in cui gli studi hanno disegni molto diversi e confronti non sempre applicabili al contesto italiano. Esistono due studi che fanno riferimento al contesto italiano di cui uno pubblicato nel 2003 e quindi datato e difficilmente utilizzabile. Tuttavia lo studio consente di identificare i *cost driver* da utilizzare per risalire al *full costing* delle unità di plasma, di piastrine o sangue intero. Questi driver sono identificabili in: tempo di lavorazione del personale, materiale diagnostico, personale sanitario che somministra il prodotto in fase pre-ospedaliera, materiale sanitario vario, attrezzature, e costi generali. Lo studio di Nardi et al (2013) stima invece un costo di €186 per unità di globuli rossi, €115 per una unità di piastrine e €60 per unità di plasma.	Da considerare anche i costi degli strumenti per la conservazione degli emocomponenti/derivati e logistica.

Qualità delle prove relative alle risorse necessarie

Qual è la qualità delle prove relative alle risorse necessarie (costi)?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Molto bassa ● Bassa ○ Moderata ○ Alta ○ Nessuno studio incluso	Tutti gli studi inclusi nella revisione non presentavano elementi sufficienti per poter essere considerati generalizzabili al contesto italiano.	

Costo-efficacia

L'analisi di costo efficacia favorisce l'intervento o il confronto?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ È in favore del confronto ○ Probabilmente è in favore del confronto ○ Non è in favore né del confronto né dell'intervento ● Probabilmente è in favore dell'intervento ○ È in favore dell'intervento ○ Varia ○ Nessuno studio incluso	Sono stati individuati 34 lavori e ne sono stati inclusi 4. In generale non è possibile stabilire con precisione quale fluido risulti più costo efficace rispetto alle alternative, inoltre alcuni degli studi inclusi hanno una qualità di reporting delle evidenze piuttosto bassa. È stata condotta una revisione sistematica su Medline ed Embase. Sono stati individuati 34 studi costo efficacia che confrontano diverse tecniche e diverse metodiche. Dopo l'applicazione dei criteri di inclusione ne sono stati considerati 4. In generale non è possibile stabilire con precisione quale fluido risulti più costo- efficace rispetto alle alternative, inoltre alcuni degli studi inclusi hanno una qualità di reporting delle evidenze piuttosto bassa. Tutti gli studi inclusi nella revisione non presentavano elementi sufficienti per poter essere considerati generalizzabili rispetto al contesto italiano.	

Equità Quale sarebbe l'impatto in termini di equità?		
GIUDIZI	**RICERCA DELLE PROVE**	**CONSIDERAZIONI AGGIUNTIVE**
○ Riduce l'equità ○ Probabilmente riduce l'equità ○ Probabilmente nessun impatto ● Probabilmente migliora l'equità ○ Migliora l'equità ○ Varia ○ Non so	Non sono stati identificati studi relativi al contesto internazionale e italiano.	Da considerare che l'utilizzo eventuale e generalizzato di sangue intero potrebbe influenzare negativamente la disponibilità di piastrine per altri pazienti (anche non traumatologici).
Accettabilità L'intervento è accettabile per i principali stakeholders?		
GIUDIZI	**RICERCA DELLE PROVE**	**CONSIDERAZIONI AGGIUNTIVE**
○ No ○ Probabilmente no ● Probabilmente si ○ Si ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 535 records relativi all'accettabilità/fattibilità della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero con 4 studi inclusi (vedi appendice H).	Riguardo alla accettabilità di emocomponenti ed emoderivati ci potrebbero essere divergenze di vedute da parte dei destinatari.
Fattibilità È fattibile l'implementazione dell'intervento?		
GIUDIZI	**RICERCA DELLE PROVE**	**CONSIDERAZIONI AGGIUNTIVE**

○ No ○ Probabilmente no ● Probabilmente si ○ Si ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 535 records relativi all'accettabilità/fattibilità della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero con 19 studi inclusi (vedi **appendice H**).	• Rilevanti problemi legati al confezionamento e fornitura di emocomponenti ed emoderivati in relazione anche alla attuale organizzazione dei centri trasfusionali/poli di produzione. • Sangue intero al momento non disponibile come emocomponente a norma (CNS in fase di revisione della indicazione). • Coinvolgimento servizi trasfusionali locali nella pianificazione e implementazione dei protocolli (logistica/organizzazione).

RIASSUNTO DEI GIUDIZI

	GIUDIZI						
PROBLEMA	No	Probabilmente no	Probabilmente si	**Sì**		Varia	Non so
EFFETTI DESIDERABILI	Irrilevanti	Piccoli	Moderati	**Grandi**		Varia	Non so
EFFETTI INDESIDERABILI	Grandi	**Moderati**	Piccoli	Irrilevanti		Varia	Non so
QUALITA' DELLE PROVE	Molto bassa	**Bassa**	Moderata	Alta			Nessuno studio incluso
VALORI	Importante incertezza o variabilità	**Probabilmente importante incertezza o variabilità**	Probabilmente nessuna importante incertezza o variabilità	Nessuna importante incertezza o variabilità			
BILANCIO DEGLI EFFETTI	A favore del confronto	Probabilmente a favore del confronto	Non è favorevole né al confronto né all'intervento	**Probabilmente a favore dell'intervento**	A favore dell'intervento	Varia	Non so
RISORSE NECESSARIE	Costi elevati	**Costi moderati**	Costi e risparmi irrilevanti	Risparmi moderati	Grandi risparmi	Varia	Non so
QUALITA' DELLE PROVE RELATIVE ALLE RISORSE NECESSARIE	Molto bassa	**Bassa**	Moderata	Alta			Nessuno studio incluso
COSTO EFFICACIA	A favore del confronto	Probabilmente a favore del confronto	Non è favorevole né al confronto né all'intervento	**Probabilmente a favore dell'intervento**	A favore dell'intervento	Varia	Nessuno studio incluso
EQUITA'	Riduce l'equità	Probabilmente riduce l'equità	Probabilmente nessun impatto sull'equità	**Probabilmente aumenta l'equità**	Aumenta l'equità	Varia	Non so
ACCETTABILITÀ	No	Probabilmente no	**Probabilmente sì**	Sì		Varia	Non so
FATTIBILITÀ	No	Probabilmente no	**Probabilmente sì**	Si		Varia	Non so

Tipo di raccomandazione

N. 23

Raccomandazione forte contro l'intervento	Raccomandazione condizionata contro l'intervento	Raccomandazione condizionata per l'intervento o per il confronto	Raccomandazione condizionata a favore dell'intervento	Raccomandazione forte a favore dell'intervento
○	○	○	○	●

N. 24

Raccomandazione forte contro l'intervento	Raccomandazione condizionata contro l'intervento	Raccomandazione condizionata per l'intervento o per il confronto	**Raccomandazione condizionata a favore dell'intervento**	Raccomandazione forte a favore dell'intervento
○	○	○	●	○

CONCLUSIONI

Raccomandazione

Racc 23. Nel paziente traumatizzato con emorragia si raccomanda in sede pre-ospedaliera l'utilizzo dei cristalloidi per il recupero della volemia, se gli emocomponenti non sono disponibili [Raccomandazione forte, qualità delle prove bassa].

Racc 24. Nel paziente traumatizzato con emorragia in sede pre-ospedaliera, quando possibile, considerare la trasfusione di emocomponenti [Raccomandazione condizionata, qualità delle prove bassa].

Giustificazione

Tenendo conto delle possibili difficoltà organizzative e logistiche, i cristalloidi rappresentano la strategia da adottare in caso di indisponibilità di emocomponenti. L'utilizzo degli emocomponenti il più precocemente possibile (incluso l'ambito pre-ospedaliero) non risponde alla necessità di espansione volemica ma di trattamento precoce e ottimale dello shock e della coagulopatia.

La raccomandazione condizionata 24 tiene conto delle potenziali difficoltà organizzative e logistiche inerenti l'utilizzo pre-ospedaliero degli emocomponenti. Tuttavia, alla luce della recente letteratura e dei presupposti fisiopatologici, il panel ritiene che l'implementazione della trasfusione pre-ospedaliera degli emocomponenti sia un obiettivo da perseguire da parte delle organizzazioni sanitarie. La tipologia di obiettivi è coerente con una organizzazione del soccorso pre-ospedaliero fortemente medicalizzato, il che consente il trasporto nella sede più appropriata, non più vicina, e l'utilizzo di emocomponenti rientra in questo approccio. Ciò implica il coinvolgimento preminente dei servizi trasfusionali operanti nel contesto dei punti ospedalieri nodali della rete traumatologica.

Le evidenze della letteratura suggeriscono l'associazione di globuli rossi e fattori della coagulazione per la prevenzione della coagulopatia. Allo stato attuale l'utilizzo del plasma in sede preospedaliera è stato effettuato prevalentemente con prodotti liofilizzati non disponibili in Italia. Sono in corso studi sull'associazione di Globuli Rossi con fattori della coagulazione, ma con evidenze ancora limitate. Il sangue intero a basso titolo anticorpale potrebbe rappresentare l'evoluzione futura del supporto trasfusionale del trauma maggiore. Al momento non è disponibile in Italia per la normativa vigente, ma sono previsti studi con l'autorità competente che valuterà la fattibilità di tale trattamento.

Non esistono trials di confronto fra cristalloidi e nessun intervento in caso di shock emorragico, ma i presupposti clinici e fisiopatologici suggeriscono la necessità di un trattamento volto a migliorare la perfusione tessutale.

Racc 23: vedi raccomandazioni precedenti (21-22) per quanto concerne volumi di infusione e target pressori.

Considerazioni relative ai sottogruppi

Nonostante alcuni risultati degli studi randomizzati suggeriscano l'utilizzo delle soluzioni saline ipertoniche ad alta concentrazione in specie nel sottogruppo di pazienti ipotesi con trauma cranico severo concomitante, robuste evidenze osservazionali riportano eventi avversi severi derivati dal loro impiego, tanto che normalmente non vengono usate in fase di emergenza pre-ospedaliera.

Considerazioni per l'implementazione

Addestramento del personale all'impiego di emocomponenti nel pre-ospedaliero.
Adozione di standard e indicatori di qualità validati a livello internazionale (rif: https/: www.blood.gov.au/pbm-guidelines; steering group of NW RTC major Haemorrhage guidelines group.toolkin for the management of major haemorrhage; BSH hemathology audit template)
Coinvolgimento centro trasfusionale per pianificazione dei protocolli, con particolare riguardo alla conservazione, trasporto e reso in caso di non utilizzo, nonché alla prevenzione e notifica di eventi avversi.
Necessità di approvazione dell'utilizzo in Italia del sangue intero.

Monitoraggio e valutazione

-

Priorità della ricerca

Utilizzo pilotato e in contesto di ricerca di sangue intero in trauma center ad alto volume.

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Appendice A – Quesito clinico e strategia di ricerca

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

Review question: What is the best volume expansion fluid to use in the resuscitation of haemorrhagic shock?	
Objective: To determine what type of fluid replacement should be used in the management of shock for children, young people and adults who have experienced a traumatic incident.	
Population	Children, young people and adults who have experienced a traumatic incident.
Intervention	Red blood cells Fresh frozen plasma Liquid plasma Crystalloids Lyophilised plasma Low Titer 0-negative Whole Blood
Comparison	A comparison or combination of the above (including different ratios)
Outcomes	Critical: Mortality at 24 hours, 30 days/1month and 12 months Health related quality of life Length of intensive care stay Adverse effects: (check SHOT website for acute transfusion reactions) Acute transfusion reaction: Haemolytic transfusion reaction – acute Haemolytic transfusion reaction – delayed Post transfusion purpura Previously uncategorised complications of transfusion Transfusion associated graft versus host disease Transfusion associated circulatory overload Transfusion associated dyspnoea Transfusion related acute lung injury Transfusion transmitted infections Important: Time to definitive control of haemorrhage Patient- reported outcomes: return to normal activities psychological wellbeing) Population size and directness: No limitations on sample size Studies with indirect populations will not be considered.
Exclusion	People with a major trauma resulting from burns. Patients in shock, not from trauma.
Search strategy	Databases: Medline, Embase, the Cochrane Library Date: All years Language: Restrict to English only Study designs: RCTs or Systematic reviews of RCTs; cohorts

The review strategy	Quality of life data: Collect all data for the stated QoL measure, for meta-analysis and GRADE report only overall scores. Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE.
Analysis	Stratify by age: children (0-17 years), adults (18 and over) Sub-groups if between-study heterogeneity: Subgroup children by: neonate (<28 days), infant (to 1 year), child (1-15 years), young people(16-17 years) Sub-group adults by: 18- 65 years and > 65 years. Within-study confounders (if cohorts used) Age Injury severity Depth of shock Degree of head injury

Standard major trauma POPULATION

Medline search terms

1.	(trauma* or polytrauma*).ti,ab.
2.	((serious* or severe* or major or life threaten*) adj3 (accident* or injur* or fall*)).ti,ab.
3.	multiple trauma/
4.	wounds, gunshot/ or wounds, stab/ or accidents, traffic/ or accidental falls/ or blast injuries/ or accidents, aviation/
5.	((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike* or head on or pile up) adj3 (accident* or crash* or collision* or smash*)).ti,ab.
6.	(mvas or mva or rtas or rta).ti,ab.
7.	(stabbed or stabbing or stab or gunshot* or gun or gunfire or firearm* or bullet* or knife* or knives or dagger).ti,ab.
8.	or/1-7

Embase search terms

1.	(trauma* or polytrauma*).ti,ab.
2.	((serious* or severe* or major or life threaten*) adj3 (accident* or injur* or fall*)).ti,ab.
3.	multiple trauma/
4.	gunshot injury/ or stab wound/ or traffic accident/ or falling/ or blast injury/ or aircraft accident/
5.	((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike* or head on or pile up) adj3 (accident* or crash* or collision* or smash*)).ti,ab.
6.	(mvas or mva or rtas or rta).ti,ab.
7.	(stabbed or stabbing or stab or gunshot* or gun or gunfire or firearm* or bullet* or knife* or knives or dagger).ti,ab.

8.	or/1-7

Cochrane search terms

#1.	MeSH descriptor: [multiple trauma] this term only
#2.	(trauma* or polytrauma*):ti,ab
#3.	((serious* or severe* or major) near/3 (accident* or injur* or fall*)):ti,ab
#4.	MeSH descriptor: [wounds, gunshot] this term only
#5.	MeSH descriptor: [wounds, stab] this term only
#6.	MeSH descriptor: [accidents, traffic] this term only
#7.	MeSH descriptor: [accidental falls] this term only
#8.	MeSH descriptor: [blast injuries] this term only
#9.	MeSH descriptor: [accidents, aviation] this term only
#10.	((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike*) near/3 (accident* or crash* or collision* or smash*)):ti,ab
#11.	(mvas or mva or rtas or rta):ti,ab
#12.	(stabbed or stabbing or stab or gunshot or gun or gunfire or firearm* or bullet or knife* or knives or dagger or shot):ti,ab
#13.	{or #1-#12}

INTERVENTION

Medline search terms

1.	*standard trauma population (see F.2.1)*
2.	hemorrhage/ or exsanguination/ or shock/ or shock, hemorrhagic/ or shock, traumatic/ or hypovolemia/
3.	(hypovol?em* or shock or exsanguin* or olig?em* or h?emorrhag* or hypoperfus*).ti,ab.
4.	(coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti,ab.
5.	(bleed* or bloodloss*).ti,ab.
6.	(blood* adj3 loss*).ti,ab.
7.	or/2-6
8.	((red blood cell* or rbc or prbc or red cell* or blood or packed cell* or erythrocyte*or fluid* or volum* or plasma*) adj5 (therap* or transfus* or replac* or resuscita* or substitut* or restor* or deficien* or replenish*)).ti,ab.
9.	exp plasma/
10.	(ffp or ((frozen or thawed or tp or fresh) adj3 plasma)).ti,ab.
11.	(albumin or zenalb or octaplas*).ti,ab.
12.	((lyophili?ed or freeze-dried or liquid or "not frozen" or "never frozen") adj3 plasma).ti,ab.
13.	(fdsp or fdp or lqp or lhp).ti,ab.

14.	exp freeze drying/ and plasma.ti,ab,sh.
15.	exp sodium chloride/
16.	exp fluid therapy/
17.	exp rehydration solutions/
18.	exp plasma substitutes/
19.	exp isotonic solutions/
20.	(sodium or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte* or plasmalyte*).ti,ab.
21.	(crystalloid* or isotonic).ti,ab.
22.	((balanced or physiologic*) adj2 (fluid* or solution*)).ti,ab.
23.	or/8-22
24.	1 and 7 and 23
25.	*blood transfusion/ or exp *blood component transfusion/ or *exchange transfusion, whole blood/ or *plasma exchange/
26.	24 or 25

Embase search terms

1.	*standard trauma population (see F.2.1)*
2.	exp *hypovolemia/ or *hemorrhagic shock/ or *traumatic shock/ or exp *bleeding/ or *exsanguination/
3.	(h?emorrhag* or hypovol?em* or shock or exsanguin* or olig?em* or hypoperfus*).ti,ab.
4.	(bleed* or bloodloss*).ti,ab.
5.	(blood* adj3 loss*).ti,ab.
6.	(coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti,ab.
7.	or/2-6
8.	exp *blood transfusion/
9.	((red blood cell* or rbc or prbc or red cell* or blood or packed cell* or erythrocyte* or fluid* or volum*) adj3 (therap* or transfus* replac* or resuscita* or substitut* or restor* or deficien* or replenish*)).ti,ab.
10.	exp *plasma/
11.	exp *blood component therapy/
12.	exp *erythrocyte transfusion/
13.	(ffp or ((frozen or fresh or thawed or tp) adj3 plasma)).ti,ab.
14.	((lyophilised or freeze-dried or liquid or "not frozen" or "never frozen") adj 2 plasma).ti,ab.
15.	(fdsp or fdp or lqp or lhp).ti,ab.
16.	exp *freeze drying/ and plasma.ti,ab,sh.
17.	exp *sodium chloride/

18.	exp *fluid therapy/
19.	exp *rehydration solutions/
20.	exp *plasma substitutes/
21.	exp *isotonic solutions/
22.	(sodium or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte* or plasmalyte*).ti,ab.
23.	(crystalloid* or isotonic).ti,ab.
24.	exp *crystalloid/
25.	((balanced or physiologic*) adj2 (fluid* or solution*)).ti,ab.
26.	or/8-25
27.	1 and 7 and 26

Cochrane search terms

#1.	*standard trauma population (see F.2.1)*
#2.	MeSH descriptor: [hemorrhage] this term only
#3.	MeSH descriptor: [exsanguination] this term only
#4.	MeSH descriptor: [shock] this term only
#5.	MeSH descriptor: [shock, traumatic] this term only
#6.	MeSH descriptor: [shock, hemorrhagic] this term only
#7.	MeSH descriptor: [hypovolemia] this term only
#8.	(haemorrhag* or hemorrhag* or hypovolem* or hypovolaem* or shock or exsanguin* or oligem* or oligaem* or hypoperfus*):ti,ab
#9.	(coagulopath* or (abnormal* near/2 coagulation) or hyperfibrinolysis):ti,ab
#10.	(bleed* or bloodloss*):ti,ab
#11.	blood* near/3 loss*:ti,ab
#12.	{or #2-#11}
#13.	((red blood cell* or rbc or prbc or red cell* or blood or packed cell* or erythrocyte*or fluid* or volum* or plasma*) near/5 (therap* or transfus* or replac* or resuscita* or substitut* or restor* or deficien* or replenish*)):ti,ab
#14.	MeSH descriptor: [plasma] explode all trees
#15.	((ffp or frozen or thawed or tp or fresh) near/3 plasma):ti,ab
#16.	(albumin or zenalb or octaplas*) .ti,ab.
#17.	((lyophili?ed or freeze-dried or liquid or "not frozen" or "never frozen") near/3 plasma):ti,ab
#18.	(fdsp or fdp or lqp or lhp):ti,ab
#19.	((balanced or physiologic*) near/2 (fluid* or solution*)):ti,ab
#20.	(crystalloid* or isotonic):ti,ab

#21.	(sodium or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte* or plasmalyte*):ti,ab
#22.	MeSH descriptor: [freeze drying] explode all trees
#23.	MeSH descriptor: [sodium chloride] explode all trees
#24.	MeSH descriptor: [fluid therapy] explode all trees
#25.	MeSH descriptor: [rehydration solutions] explode all trees
#26.	MeSH descriptor: [plasma substitutes] explode all trees
#27.	MeSH descriptor: [isotonic solutions] explode all trees
#28.	{or #13-#27}
#29.	#1 and #12 and #28
#30.	MeSH descriptor: [blood transfusion] this term only
#31.	MeSH descriptor: [blood component transfusion] explode all trees
#32.	MeSH descriptor: [exchange transfusion, whole blood] this term only
#33.	MeSH descriptor: [plasma exchange] this term only
#34.	{or #30-#33}
#35.	#29 or #34

Appendice B – Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

1. Caratteristiche degli studi inclusi

Tabelle delle caratteristiche degli studi. Comparazione 1. Crystalloids vs crystalloids.

SR	**Safieiko 2020**
Included studies, search update	15 studies including 3264 patients Search up to August 20th 2020
POPULATION	Human studies involved adult patients needing fluid resuscitation
INTERVENTION COMPARISON	the effect of hypertonic saline/dextran or hypertonic saline for fluid resuscitation
OUTCOMES	– Short- term survival (hospital discharge or 28 to 30 days). – long- term mortality (≥ 3 months), 24-hour mortality, overall, mortality, – adverse outcome, – length of stay in an intensive care unit and hospital, – laboratory parameters at patient admission, – the Glasgow Outcome Scale Extended score.
Language	English language
setting	Prehospital / ED
study design	Randomized controlled trial
SYBGROUP analysis	– hypertonic/dextran solutions – hypertonic solution alone
EXCLUSION	Observational studies, case control studies, non-trials conducted on simulated models, editorials, reviews, guidelines, meta-analysis, and theoretical models
Quantitative or qualitative analysis	Quantitative and qualitative

Study	**Young 2014**
Study type	Randomized controlled trial
Number of participants	46 evaluable subjects (among 65 randomized)
Settings	Patients at the University of California Davis Medical Center, level 1 trauma center
Funding	This was an investigator-initiated trial supported by Baxter Healthcare (Deerfield, IL)
Duration of study	February 2011 through February 2012
Age, gender, ethnicity	Age, year 0.9% NaCl: 39 ± 14, Plasma-Lyte 38 ± 19 Sex (male)† 0.9% NaCl :19 (79) Plasma-Lyte 16 (73)
Patient characteristics	Adult trauma patients requiring blood transfusion, intubation, or operation within 60 minutes of arrival at the University of California Davis Medical Center.
Intervention	0.90.9% NaCl (n = 24) Plasma-Lyte (n = 22) during the first 24 hours after injury
Outcomes	- change in base excess from 0 to 24 hours. - serum electrolyte levels, calculated osmolality, lactate, arterial pH, international normalized ratio, activated partial thromboplastin time, study fluid volume, and urine volume at 6 and 24 hours; - organ failure, - ventilator-free days, - occurrence of an open abdomen within 30 days; - hospital and intensive care unit length of stay; - in-hospital mortality

Study	**Rowell 2016**
Study type	Retrospective cohort study
Number of participants	1245 injured patients
Settings	Emergency department
Funding	Supported by subcontract W81XWH-08-C-0712 from the U.S. Army Medical Research and Materiel Command. Infrastructure for the Data Coordinating Center was supported by Clinical and Translational Science Awards funds of grant UL1 RR024148 from the National Institutes of Health
Duration of study	Not reported
Age, gender, ethnicity	AIS Head ≥ 3 Age (year) LR group (n=52): 45.2 – 20.8 NS group (n=256): 42.8 – 18.4 Sex (%male) LR group: 65.4 NS group: 71.9 AIS Head ≤ 2 Age (year) LR group (n=65): 41.1 – 20.1 NS group (n=418): 38.8 – 17.8 Sex (% male) LR group: 73.8 NS group 77.3
Patient characteristics	Injured patients who required the highest level activation at one of 10 level 1 trauma centers who subsequently received one or more units of red blood cells (RBC) within 6 hours of hospital admission. Data were obtained from a database created by the Center for Clinical and Translational Sciences at the University of Texas Health Science Center at Houston for the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study.
Intervention	Lactated Ringer's (LR) n=117 Nnormal saline (NS) n=674 TBI patients: 308
Outcomes	- Mortality at 30 days, - RBC and crystalloid use in the first 6 hours after admission

Tabelle delle caratteristiche degli studi. Comparazione 2. Blood components vs standard care.

SR	Rijnhout 2019	Coccolini 2019
Included studies, search update	2 RCTs (Moore 2018, Sperry 2018) + 7 retrospective studies, Search up to August 1st 2018	2 RCTs (Moore 2018, Sperry 2018) Search up to August 2018
POPULATION	Trauma patients	Trauma patients with haemorrhagic shock
INTERVENTION COMPARISON	Prehospital blood-component transfusion (PHBT)	pre-hospital plasma vs. usual care
OUTCOMES	For the primary outcomes (24-hour mortality and long-term mortality), Long-term mortality was defined as 30-day or in-hospital mortality. Secondary outcome was adverse events resulting from PHBT.	The primary outcome measures were mortality at 24 h and at 1 month. Secondary outcome was morbidity (acute lung injury and multi-organ failure).
Language	The search was not restricted by language or publication status.	The search was not restricted by language or publication status.
setting	Pre-hospital	Pre-hospital
study design	randomized and retrospective studies: cohorts with matched patients	randomized trials
Subgroup analysis	None	None
Exclusion	no blood or blood products administered, no prehospital setting, not a study in humans, no original data available. Studies containing inter-facility transports	Not reported
Quantitative or qualitative analysis	Quantitative and qualitative	Quantitative and qualitative

Study	**Grigg 2018**
Study type	Single centre retrospective observational cohort study
Number of participants	195 trauma patients
Settings	United Kingdom
Funding	No funding was received for this study
Duration of study	January 2010 and 1 February 2015
Age, gender, ethnicity	Gender: Female (n, %) Crystalloids: 26 (25) PRBC: 24 (26); Male (n, %) Crystalloids:77 (74) PRBC: 68 (73) Age (mean, SD) Crystalloids: 45 (20) PRBC: 43 (20)
Patient characteristics	Inclusion criteria: 1) blunt and/or penetrating traumatic injury with suspected traumatic haemorrhage, 2) pre-hospital Code Red declaration with transfusion of crystalloid and/or PRBC, 3) patient conveyed to an MTC, 4) traumatic cardiac arrests (TCAs) where return of spontaneous circulation (ROSC) was gained, declared Code Red and conveyed to an MTC.
Intervention	crystalloid (n = 103) PRBC (n = 92)
Outcomes	- all-cause mortality at 6 hours (h) and 28 days (d) - including a sub-analysis of patients receiving a major and massive transfusion

Study	**Neal 2012**
Study type	Prospective cohort study
Number of participants	N = 452
Settings	Conducted in USA
Funding	Academic or government funding (NIH)
Duration of study	Intervention + follow-up: In-hospital
Age, gender, ethnicity	Age - Range: 17-89. Gender (M:F): 70% male. Ethnicity: Not reported
Patient characteristics	Patients who received 10 units or more of PRBC in the first 24 hours. Inclusion criteria: Blunt mechanism of injury, systolic hypertension or elevated base deficit, blood transfusion requirements in first 12 hours and any region exclusive of the brain with an abbreviated injury score of greater than or equal to 2.
Intervention	(n=114) Intervention 1: Crystalloid: RBC - Highest. Greater than or equal to 1.5:1. Duration In hospital. (n=111) Intervention 2: Crystalloid: RBC - High. Greater than or equal to 1:1 and < 1.5:1. Duration In hospital. Concurrent medication/care: Not stated (n=113) Intervention 3: Crystalloid: RBC - Medium. Greater than or equal to 1:5:1 and < 1.1. Duration In hospital. Concurrent medication/care: Not stated (n=114) Intervention 4: Crystalloid: RBC - Low. < 0.5:1. Duration In hospital. Concurrent medication/care: Not stated
Outcomes	- Mortality at 30 days - Mortality at In hospital; - AE - Multiple organ failure, Transfusion-related acute lung injury, Acute respiratory distress syndrome, Transfusion transmitted infections

Study	**Ditillo 2018**
Study type	retrospective cohort analysis of the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) database.
Number of participants	19,643 trauma patients
Settings	USA
Funding	No funding
Duration of study	2-year (2015–2016)
Age, gender, ethnicity	Age: mean ± SD, y Cryoprecipitate (n = 4,945): 39 ± 22, No Cryoprecipitate (n = 14,698): 41 ± 22 Male, n (%) Cryoprecipitate: 3,758 (76) No Cryoprecipitate: 11,611 (79) Whites, n (%) Cryoprecipitate: 2,769 (56) No Cryoprecipitate: 8,525 (58) Hispanic, n (%) Cryoprecipitate: 643 (13) No Cryoprecipitate: 2,058 (14)
Patient characteristics	adult trauma patients who received: 4 units or greater of packed red blood cells (pRBCs) within 4 hours of admission
Intervention	Cryoprecipitate (n = 4,945) No Cryoprecipitate (n = 14,698) Patients were stratified into two groups based on the transfusion of cryoprecipitate as an adjunct of massive transfusion: those who received at least one unit of cryoprecipitate within 24 hours of admission for initial resuscitation in the emergency department (ED) and those who did not receive cryoprecipitate.
Outcomes	- 24-hour transfusion requirements, - in-hospital complications, - mortality

Tabelle delle caratteristiche degli studi. Comparazione 3. Blood components ratio.

SR	McQuilten 2018	Luz 2019	Ritchie 2020	Rodríguez 2020	Poole 2016	Rahouma 2018	Wirtz 2020
Blood components ratio	FFP:PLT:PRBC	FFP:PLT:PRBC, FFP:PRBC, PLT:PRBC	FFP:PLT:PRBC	FFP:PRBC	FFP:PRBC	FFP:PRBC	FFP:PRBC, PLT:PRBC
Included studies, search update	6 trials; search up to 21st February 2017	55 (2 trial and 53 observational), search up to July 31, 2018	7 RCTs, Search 7up to May 10, 2019	33 studies (2 clinical trials and 31 observational studies); search between the first week of 1990 and week 40 of 2019	9 observational studies; search date December 14 2014	36 stidies (2 trials, 24 observational); search up to January 10th, 2016	39 (6 trial and 33 observational), search up to
POPULATION	pediatric and/or adult who had critical bleeding (defined as major hemorrhage that is life-threatening and likely to result in the need for massive transfusion	adult trauma patients (≥15 years old) with an important risk of bleeding as per each study definition, who received at least 1 unit of RBCs within the first 24 hours postadmission.	Treated within adult emergency departments (≥14 y) Active major hemorrhage	Patients with civilian trauma massive bleeding	Severely injured patients	A large, cohort of surgical patients, including both trauma and non-trauma sub specialties.	The target population was patients 16 years of age or older with severe trauma (injury severity score [ISS] ≥16) resulting in hemorrhage, who received at least 1 unit of RBCs.
INTERVENTION COMPARISON	intervention comparisons were either dose, timing or ratio (algorithm) of blood component therapy (FFP, platelets, cryoprecipitate, or fibrinogen concentrate) to RBCs.	Intervention was the resuscitation of trauma patients using a high fixed transfusion ratio of FFP and PLTs to RBCs or FFP or PLTs to RBCs, as defined in each study. The control was a low fixed transfusion ratio of FFP and PLTs to RBCs or FFP or RBCs to RBCs, also defined and compared in each study.	Intervention: 2:1 ratio of packed red cell to fresh frozen plasma; Standard protocol with fibrinogen; Whole blood transfusion. Control: Placebo/standard therapy (1:1 ratio of packed red cells to fresh frozen plasma	The FFP:RBC ratio used was taken into account both in the intervention and in the comparator, and the accepted high ratio was that defined for each study. A 1:1 ratio represented the same number of units of FFP and RBC; in contrast, a 1:2 meant twice the amount of RBC per FFP unit, and this latter one was a lower ratio	Three different treatments aimed at contrasting coagulopathy: high fresh frozen plasma/packed red blood cells ratios, fibrinogen, and tranexamic acid administration.	Different FFP: RBC ratio, where categories were grouped as being low vs high for each study according to a predetermined ratios (1:1, 1:1.5, or 1:2) for analysis purposes	The plasma-to-RBC ratio was categorized into three groups: <1:2 (low ratio), 1-2:2 (high ratio) and > 1:1 (inverse reported more than two transfused RBC units for every plasma unit transfused. In the high-ratio group, studies were selected that reported transfusion of 1 or 2 plasma units for every 2 transfused RBC units. In the inverse-ratio group, studies were selected that reported to have given more plasma units than RBC units.

SR	McQuilten 2018	Luz 2019	Ritchie 2020	Rodríguez 2020	Poole 2016	Rahouma 2018	Wirtz 2020
OUTCOMES	mortality at 24 h and 28 days and (2) morbidity (infection, acute kidney injury, acute respiratory distress syndrome, multiorgan failure, thromboembolic events during hospital admission). Secondary outcomes were hospital and intensive care unit (ICU) length of stay, transfusion-related adverse events, correction of coagulopathy, hospital readmission, quality of life, and costs.	The primary outcome was in-hospitalmortality assessed at two time points: at 24 hours of admission and at 30 days of admission. Secondary outcomes were: 1) cumulative number of allogeneic RBCs, FFP, and PLT units transfused in 24 hours postadmission and 2) effect on the ATC, represented by values of international normalized ratio (INR), fibrinogen, and TEG or ROTEMvariables, allmeasuredwithin 24 hours postadmission.	Primary—mortality; Secondary—length of stay in hospital, complications, total transfusion requirements	Mortality before 24hours was considered early and at 30 days late.	Mortality	Primary outcomes were 24-hr mortality and 30-day/in-hospital mortality for high vs low FFP: RBC ratio in the whole cohort while secondary outcomes were mortality differences around the different cut-off ratios (1:1, 1:1.5, or 1:2) in order to identify the most beneficial ratio, morbidity outcomes (including ARDS and ALI) and lengths of hospital stay (LOS).	The main outcome of this study is the development of thromboembolic events.
language	Searches were not restricted by language or publication status.	The search was not restricted by date, language, or publication status.	not specified	no language restrictions	we applied English-language restriction	Studies written in English	Only articles written in English, German, and Dutch were included.
setting	not specified	not specified	ED	not specified	not specified	Twenty-eight studies were from civilian hospitals, 4 from military settings, and 4 from combined civilian/military settings.	not specified
study design	randomized controlled trial	This review included prospective and retrospective cohort studies with a control group (e.g., observational studies comparing high vs. low transfusion ratios) and randomized controlled trials (RCTs).	Randomized controlled trial	clinical controlled trials or observational cohort, case controlled, studies	We selected only studies that included a study and a control group, including randomized controlled trials (RCTs) and observational studies only if adjustment for confounders was performed (e.g. logistic regression, matching)	Randomized controlled trial or observational studies	Randomized controlled trials (RCTs) and observational studies
SYBGROUP analysis							Trauma and non-trauma population

SR	McQuilten 2018	Luz 2019	Ritchie 2020	Rodríguez 2020	Poole 2016	Rahouma 2018	Wirtz 2020
EXCLUSION	not specified	We excluded observational studies that addressed other approaches such as transfusion guided by viscoelastic methods or studies that addressed the use of other concentrate of clotting factors. Case reports, case series, and conference proceedings were also excluded.	Pediatric (<14 y); Post partum hemorrhage; Intracranial hemorrhage; cost effectiveness; other study design	Any studies with the following characteristics were excluded: (a) studies such as case reports or case series; (b) studies using a historical cohort as the comparator; (c) studies that failed to consider the severity of the patients using scales such as the Injury Severity Score (ISS); and (d) studies, including patients with war or military trauma, or that included patients undergoing programmed surgeries.	We did not include letters, case reports, and observational studies without controls and adjustment for important covariates. Studies on children (age≤16) were excluded. We excluded as well studies focusing on specific conditions such as head bleeding, considering instead abdominal, thoracic, pelvic bleeding, and coagulopathy in general. We excluded traumatic brain injury because of the great prognostic weight carried by even modest bleeding and because the outcome of choice in our review, mortality, is not suitable for traumatic brain injury studies for which a composite outcome including death, vegetative status, and severe disability is preferable. Bleeding or coagulopathy from other causes (as obstetrical or perioperative) were not considered.	not specified	If the number of transfused blood components or the use of pro-coagulant medication was not reported, studies were excluded from analysis. Reviews, correspondences, editorials, experimental (animal) studies and case reports/series were excluded. Studies on burn victims were also excluded because of the difference in fluid management in this particular population.
Trials inclusi per la comparazione 20	2 RCT	2 RCT	2 RCT	31 observational studies	8 observational studies	32 observational studies	2 observational studies
Quantitative or qualitative analysis	Quantitative and qualitative	Quantitative	Only qualitative	Quantitative	Quantitative and Qualitative	Quantitative and qualitative	Quantitative

Study	Butler 2019
Study type	Retrospective cohort study
Number of participants	N=583
Settings	Level I and II pediatric trauma centers participating in the Trauma Quality Improvement Program
Funding	Dr. Butler is supported by the Department of Health and Human Services T-32 Pediatric Injury Research Training Program at the Harborview Injury Prevention and Research Center (5T32HD057822-09).
Duration of study	Pediatric Trauma Quality Improvement Program Database from 2014 to 2016
Age, gender, ethnicity	Age [median (IQR)]: 5 (2-10) Gender (% F): 40% Ethnicity: not reported
Patient characteristics	Patients included in the database are those under 18 years who sustained a traumatic injury and were either admitted to the trauma facility or died while at the facility. The study population consisted of pediatric trauma patients (≤14 years old) receiving massive transfusion as documented in the pediatric TQIP database from 2014–2016. Massive transfusion was defined as ≥40 mL/kg of total blood products within the first 24h (17). Patients were excluded if they had a non-traumatic mechanism or an unknown outcome. To mitigate survival bias, patients who died within the first 30 minutes of arrival were excluded, thus removing those patients with a low FFP:PRBC ratio due to inadequate time to receive FFP. Patients who did not receive any PRBC were also excluded, because the primary independent variables could not be calculated due to division by zero.
Intervention	FFP:PRBC ratio and platelet:PRBC ratio. The FFP:PRBC and platelet:PRBC ratios were calculated by dividing the number of units of FFP or platelets by the number of units of PRBC. The patients were divided into three groups based on their FFP:PRBC ratio at 24h: low (<1:2) (n=232), medium (≥1:2 and <1:1) (n=215) and high (≥1:1) (n=136), and into three groups based on their platelet:PRBC ratio at 24h: none (0) (n=225), low (>0 and <1:2) (n=286), and high (≥1:2) (n=72).
Outcomes	The primary outcome was 24h mortality. Secondary outcomes included in-hospital mortality and a predetermined list of complications. Hospital length of stay, intensive care unit (ICU) length of stay, ventilator days, and hospital disposition were evaluated for surviving patients.

Study	**Cannon 2017**
Study type	Cohort study
Number of participants	N=352
Settings	Department of Defense Trauma Registry (DoDTR) - US combat support hospitals in Iraq and Afghanistan
Funding	Not reported
Duration of study	Between 2001 and 2013
Age, gender, ethnicity	Age [median (IQR)]: LOW Ratio: 7 (4-10); HIGH Ratio: 9 (5-12) Gender (% F): LOW Ratio: 30.8%; HIGH Ratio: 26.4% Ethnicity: not reported
Patient characteristics	All injured patients **younger than 18** years admitted to US combat support hospitals in Iraq and Afghanistan from 2001 to 2013 were included. To clearly identify a cohort of patients at risk of death from acute hemorrhage, we excluded all patients with a severe isolated head injury (head Abbreviated Injury Scale [AIS] score ≥3 with no other injuries) or a predominant head injury (head AIS score of 2 or more over the next highest AIS) from the analysis; subset analysis was performed with these patients included as well. Patients with predominant thermal injury and those with non-traumatic mechanisms (e.g., drowning and asphyxiation) were also excluded. We also excluded older children (age, 15–17 years) to focus on those with purely pediatric physiology. MT was defined as 40 mL/kg or greater total blood products received within the first 24 hours of injury.30 Those patients who did not receive a MT were excluded unless the patient died within 24 hours despite receiving any blood products, thereby mitigating the risk of introducing survival bias into our analysis. This left us with a final cohort of very young, critically injured patients at high risk of death from haemorrhage.
Intervention	Two patient cohorts were defined using the current Trauma Quality Improvement Program definitions as low PLAS/PRBC (<1:2) (n=65) and high PLAS/PRBC (≥1:2) (n=299). An alternative definition of LO less than 1:1 and HI of 1:1 or less was also evaluated.
Outcomes	- 24-hour and in-hospital mortalities - Length of stay (LOS), intensive care unit (ICU) free days, need for mechanical ventilation, and ventilator-free days

Study	**Cunningham 2019**
Study type	Retrospective study
Number of participants	N=465
Settings	American College of Surgeons Pediatric Trauma Quality Improvement Program (ACS TQIP-P) data bank.
Funding	Not reported
Duration of study	Data fromJanuary 2015 to December 2016were analyzed
Age, gender, ethnicity	Age [median (IQR)]: LOW ratio: 8 (2-15), MEDIUM ratio: 7 (3-15), HIGH ratio: 7 (0-17) Gender (% F): LOW ratio: 32%; MEDIUM ratio: 42%, HIGH ratio: 28% Ethnicity: not reported
Patient characteristics	Pediatric trauma patients **≤18 y**, who received RBC within 24 h of admission and were also massively transfused according to the definition 40 mL/kg total blood product received within 24 h of admission. The patient age range was chosen according to the ages available in the TQIP-P data set (0-18 y) and the age ranges used in previous studies. Patients excluded had no signs of life on arrival, presented with burn as their primary diagnosis, or had an abbreviated injury scale (AIS) score of 6 (unsurvivable injury) in any body region and subsequently died. Also of note, there were no patients with burn diagnosis once those not transfused RBC were excluded.
Intervention	Plasma:RBC and platelet:RBC ratios were calculated using blood volume at 4 and 24 h from admission. Patients were classified into one of three groups for both plasma and platelets; low (<1:2) (n=376), medium (≤1:2 to <1:1) (n=64), and high (≥1:1) (n=25). Plasma and platelet ratios were independently evaluated according to the three cohort ratios to reflect the methodology of the PROMMTT trial and other pediatric studies looking at blood product ratio during massive transfusion.
Outcomes	Patient outcomes included ventilator, intensive care unit (ICU), and hospital-free days, in-hospital complication rates (acute kidney injury, acute respiratory distress syndrome, severe sepsis, infection, deep venous thrombosis/pulmonary embolism), hemorrhage control procedure rates, and mortality rates.

Study	Haltmeier 2017
Study type	Retrospective observational study
Number of participants	N=385
Settings	Blood bank database of the Los Angeles County and University of Southern California (LAC+USC) Medical Center
Funding	Not reported
Duration of study	2002-2011
Age, gender, ethnicity	Age [median (IQR)]: 32 (2-50) Gender (% F): 28.6 Ethnicity: not reported
Patient characteristics	Patients of all ages with isolated severe blunt traumatic brain injury (TBI) that received PRBC transfusion within the first 24 hours after hospital admission were included. Isolated severe TBI was defined as an Abbreviated Injury Scale (AIS) head score ≥3 and an AIS chest, abdomen, extremities and external score < 3. Patients with cardiac arrest in the Emergency Department (ED), defined as a systolic blood pressure (SBP) of 0 mmHg, were excluded from the analysis, as mortality in these cases was assumed not to be related to coagulopathy.
Intervention	Transfusion ratios were calculated as the number of plasma units to PRBC units (plasma:PRBC) (n=242) and PLT units to PRBC units (PLT:PRBC) (n=111) transfused. Transfusion ratios were then dichotomized using the transfusion of at least one unit plasma per unit PRBC (plasma:PRBC ≥ 1) and at least one unit PLT per unit PRBC (PLT:PRBC ≥ 1) as the cut-off value.
Outcomes	In-hospital mortality

Study	Nederpelt 2019
Study type	Retrospective nationwide cohort study
Number of participants	N=4427
Settings	The American College of Surgeons (ACS) TQIP database
Funding	Not reported
Duration of study	2013 to 2016
Age, gender, ethnicity	Age (mean): 41 Gender (% F): 21% Ethnicity: 43% Non-hispanic white, 30% Black
Patient characteristics	All trauma patients 18 years or older who required at least 10 units (3,000 CCs) of pRBC and at least 1 unit (300 CCs) of FFP in the first 24 hours of admission were included. All transfer patients, and those with incorrect or missing transfusion data, as per the TQIP coding rules in the Participant Use File and National Trauma Data Standard were excluded. In order to decrease the chance of FFP delay and survival bias, all patients who died in the emergency room, as well as those whose FFP:pRBC ratio was different in the first 4 vs 24 hours of hospitalization, were excluded.
Intervention	Different FFP:pRBC ratios: the ratio of FFP to pRBC was calculated and patients were assigned to 7 ratio cohorts (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, and over 1:6]).
Outcomes	Primary outcome was 24-hour mortality. Secondary outcomes included in-hospital mortality, need for surgical intervention, unplanned return to the operating room (OR), infectious complications (surgical site infections [SSIs], ventilatorassociated pneumonia, sepsis, extremity compartment syndrome, acute respiratory distress syndrome [ARDS]), ICU length of stay, and discharge disposition.

Study	**Sehdev 2020**
Study type	Retrospective database analysis
Number of participants	N=239
Settings	The Trauma Quality Improvement Program (TQIP) database, a national de-identified database backed by the American College of Surgeons with 825 participating trauma centers across the USA.
Funding	No funding was received for this work.
Duration of study	2014 to 2016
Age, gender, ethnicity	Age [median (IQR)]: BR: 14 (6), UR: 12 (9) Gender (% F): BR: 30.5%, UR: 29.6% Ethnicity: BR: 38.2% black, 48.2% white, 5.6% Asian, 16% Hispanic; UR: 31.2% black, 54.1% white, 1.9% Asian, 22.4% hispanic
Patient characteristics	**Pediatric** trauma patients < 18 years old receiving a massive transfusion (MT) after trauma. For this study, MT was defined as receiving ≥ 6 units of PRBC within 24 h. Patients with no documented data on blood product transfusion were excluded.
Intervention	We compared PTPs receiving PRBC: plasma ratio of > 2:1 (UR, n=98) versus ≤ 2:1 (BR, n=141). An additional analysis of severely UR of ≥ 4:1 PRBC: plasma and BR of ≤ 2:1 was also performed.
Outcomes	The primary outcome was mortality. In addition, we evaluated total hospital length-of-stay (LOS), intensive care unit (ICU) LOS, ventilator days, discharge disposition, and other complications including acute kidney injury (AKI), pneumonia, deep venous thrombosis (DVT), acute respiratory distress syndrome (ARDS), and cardiac arrest.

Tabelle delle caratteristiche degli studi. Comparazione 4 Whole blood vs component therapy.

SR	McQuilten 2018	Crowe 2020	Avery 2020	Cruciani 2020	Malkin 2020	Ritchie 2020
Included studies, search update	6 trials; search up to 21st Februa\ry 2017	12 studies: retrospective cohort (n = 10), prospective cohort (n = 1), and randomized control trial (n =1); search from January 2007 to June 2019.	Six studies: 1 prospective randomised trial, 1 prospective with historical controls, 4 retrospective analyses. from the inception of the databases to the search date (15th December 2019).	7 studies: 1 RCT, 6 observational. latest search March 6, 2020	5 studies: 1 RCT, 4 OBS retrospective; search up to 2018	7 RCTs, Search 7up to May 10, 2019
POPULATION	pediatric and/or adult who had critical bleeding (defined as major hemorrhage that is life-threatening and likely to result in the need for massive transfusion	patients experiencing hemorrhagic shock due to trauma,	Human subjects aged ≥16 years requiring emergent uncrossmatched blood following traumatic injury.	massive trauma bleeding	adult trauma patients with hemorrhagic shock who require blood transfusion	Treated within adult emergency departments (≥14 y) Active major hemorrhage
INTERVENTION COMPARISON	intervention comparisons were either dose, timing or ratio (algorithm) of blood component therapy (FFP, platelets, cryoprecipitate, or fibrinogen concentrate) to RBCs.	whole blood transfusion compared with component therapy (We defined component therapy as combinations of apheresis platelets (aPLT), packed red blood cells, fresh frozen plasma, and fresh whole blood)	use of WB transfusion compared with blood component therapy	whole blood in massive trauma bleeding, and that whole blood transfusion was compared to transfusion of blood component.	WB resuscitation compared to resuscitation with blood compo- nents in balanced ratios. We included all types of WB - FWB as well as cold stored whole blood. The control group had to receive 1:1:1 blood component resuscitation including platelets, since we feel compar- ing WB to RBCs and plasma alone introduces a source of confound- ing.	Intervention: 2:1 ratio of packed red cell to fresh frozen plasma; Standard protocol with fibrinogen; Whole blood transfusion. Control: Placebo/standard therapy (1:1 ratio of packed red cells to fresh frozen plasma
OUTCOMES	mortality at 24 h and 28 days and (2) morbidity (infection, acute kidney injury, acute respiratory distress syndrome, multiorgan failure, thromboembolic events during hospital admission). Secondary outcomes were hospital and intensive care unit (ICU) length of stay, transfusion-related adverse events, correction of coagulopathy,	24-hour mortality, in-hospital mortality, and 30-day mortality	survival at 30 days. Secondary outcomes were in-hospital mortality, 24 hours mortality, total volume of transfusion, morbidity including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI),	mortality (30-day/in-hospital and 24-h mortality) and adverse events/transfusion reactions	24 hour and 30-day survival, blood product utilization and adverse events.	Primary—mortality; Secondary—length of stay in hospital, complications, total transfusion requirements

SR	McQuilten 2018	Crowe 2020	Avery 2020	Cruciani 2020	Malkin 2020	Ritchie 2020
	hospital readmission, quality of life, and costs.		multiple organ dysfunction syndrome (MODS), embolic events and transfusion reactions.			
language	Searches were not restricted by language or publication status.	no language restriction	Non-English language papers were excluded	not specified	We only included studies in English, Russian or Hebrew that were published as full reports	not specified
setting	not specified	We included studies from both civilian (7 studies) and military settings		prehospital/ED setting	not specified	ED
study design	randomized controlled trial	randomized control trials, non-randomized control trials, and retrospective or prospective cohort studies with comparison groups.	Randomised controlled trials. Prospective or retrospective observational cohort studies	randomized clinical trial (RCT) and observational studies published in the last 20 years (2000–2020).	randomized and non-randomized controlled trials as well as retrospective observational studies	Randomized controlled trial
SYBGROUP analysis			TBI patients			
EXCLUSION	not specified	case reports, opinion pieces, review articles, and studies involving non-human subjects. We did not include abstracts.	abstracts and other non-published data were excluded	studies enrolling less than ten patients and studies evaluating pediatric patients were excluded.	not specified	Pediatric (<14 y); Post partum hemorrhage; Intracranial hemorrhage; cost effectiveness; other study design
Trials inclusi per la comparazione 20	1 RCT	1 RCT, 11 OBS	1 RCT, 5 OBS	1 RCT, 6 OBS	1 RTC, 4 OBS	2 RCTs
Quantitative or qualitative analysis	Quantitative and qualitative	Quantitative and qualitative	Only qualitative	Quantitative and qualitative	Only qualitative	Only qualitative

Study	**Cotton 2013**
Study type	Randomized controlled trial
Number of participants	107 adults patients who were randomized (n Whole blood=55; n component therapy=52)
Settings	Texas Trauma Institute at Memorial Hermann Hospital - American College of Surgeons–verified level I trauma center.
Funding	Supported by a grant from the Department of Defense via W81XWH-08-C-0712
Duration of study	Not reported
Age, gender, ethnicity	N WB group: median age, yr 40 (29, 56); Male sex (%) 78; White race (%) 60 N component therapy: median age yr 38 (25, 56); Male sex (%) 83; White race (%) 52
Patient characteristics	Early resuscitation of injured adult patients presenting with evidence of hemorrhagic shock and predicted to receive a large volume transfusion. There were no differences in mechanism of injury (69% blunt in mWB vs 67% in COMP; P = 0.84), nor method of transport (71% of mWB arrived by helicopter vs 65% of COMP; P = 0.60) Although arrival vital signs and overall injury severity were similar, the mWB group did demonstrate a trend toward lower arrival Glasgow Coma Scale scores (P = 0.11) and higher head AIS score (median 0 with 0 and 3 IQR vs 0 with 0 and 2 IQR, P=0.14).
Intervention	Whole blood versus standard component therapy (red blood cells, plasma, and platelets)
Outcomes	- 24-hour blood product use (RBC, plasma, and platelets transfused in the first 24 hours) - 24-hour and 30-day mortality, - Length of stay, - transfusion associated complications, - infections.

Study	**Leeper 2020**
Study type	A propensity-matched cohort study
Number of participants	28 whole blood recipients were matched to 28 conventional component patients who did not receive whole blood
Settings	Prehospital/emergency department
Funding	Not reported
Duration of study	Patient data were collected for the propensity analysis in 2 parts. First, the trauma database was queried to identify injured children (age <18 years) who presented to the hospital between January 2013 and May 2016 and received a transfusion of at least 1 blood product in the ED. These patients formed the conventional components group. Second, the trauma database was queried to identify injured children age <18 years who received whole blood during their initial resuscitation between June 2016 and May 2019, the time period after the practice change where whole blood replaced RBC as the recommended initial trauma resuscitation product. These patients formed the whole blood group.
Age, gender, ethnicity	Age (yr) LTOWB: 11 (5–14) Components: 8 (3–13) 0.87 Sex: Female LTOWB: 9/28 (32%), Components: 11/28 (39%); Male LTOWB: 19 /28 (68%), Components: 17/28 (61%) Race/ethnicity: White LTOWB: 20/28 (72%) Components: 21/28 (75%); Black LTOWB: 5/28 (17%) Components: 5/28 (18%); Other/Not specified LTOWB: 3/28 (11%) Components: 2/28 (7%)
Patient characteristics	Injured children, age ≥1 year
Intervention	Low Titer Group O Whole Blood Transfusion or component therapy
Outcomes	- time to resolution of base deficit, - product volumes transfused, - incidence of persistent post-transfusion - coagulation dysregulation - functional disability at discharge (defined by a functional independence measure score of dependent in any category or discharge to a rehabilitation facility), - hospital length of stay (LOS), intensive care unit (ICU) LOS, - time receiving mechanical ventilation, - total transfusion volume.

2. Lista degli esclusi con motivazione

	Study	Reason
1	Gu 2020 - Restricted fluid resuscitation improves the prognosis of patients with traumatic hemorrhagic shock	Wrong intervention
2	Zhang 2018 - Clinical effects of two types of fluid infusion in pre-hospital care for traumatic shock	No outcome of interest- outcomes already included in SR
3	Matsuyama, 2018 - Preoperative fluid restriction for trauma patients with hemorrhagic shock decreases ventilator days	Wrong intervention
4	Harada 2017 - 10-Year trend in crystalloid resuscitation: Reduced volume and lower mortality	Wrong intervention
5	Garrigue 2017 - French lyophilized plasma versus fresh frozen plasma for the initial management of trauma-induced coagulopathy: a randomized open-label trial	Wrong intervention
6	Heuer 2014 - Prehospital fluid management of abdominal organ trauma patients—a matched pair analysis	Wrong intervention
7	Doughty 2018 - Massive transfusion: changing practice in a single Norwegian centre 2002–2015	Wrong intervention
8	Zander 2014 - Does resuscitation with plasma increase the risk of venous thromboembolism?	Wrong intervention
9	Rosenfeld 2019 - Defining massive transfusion in civilian pediatric trauma	Wrong intervention
10	Schreiber 2015 - A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial	Wrong intervention
11	Crescenzo 2017 - Prehospital hypertonic fluid resuscitation for trauma patients: A systematic review and meta-analysis	Not updated reviewed Complete overlapping with other reviews
12	Hazelton 2020 - Cold-stored whole blood: A better method of trauma resuscitation?	No outcome of interest- outcomes already included in SR
13	Hanna 2020 - Nationwide analysis of whole blood hemostatic resuscitation in civilian trauma	No outcome of interest- outcomes already included in SR
14	Cardena 2018 - Platelet transfusions improve hemostasis and survival in a substudy of the prospective, randomized PROPPR trial	No outcome of interest- outcomes already included in SR
15	Shea 2020 - The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage	No outcome of interest- outcomes already included in SR

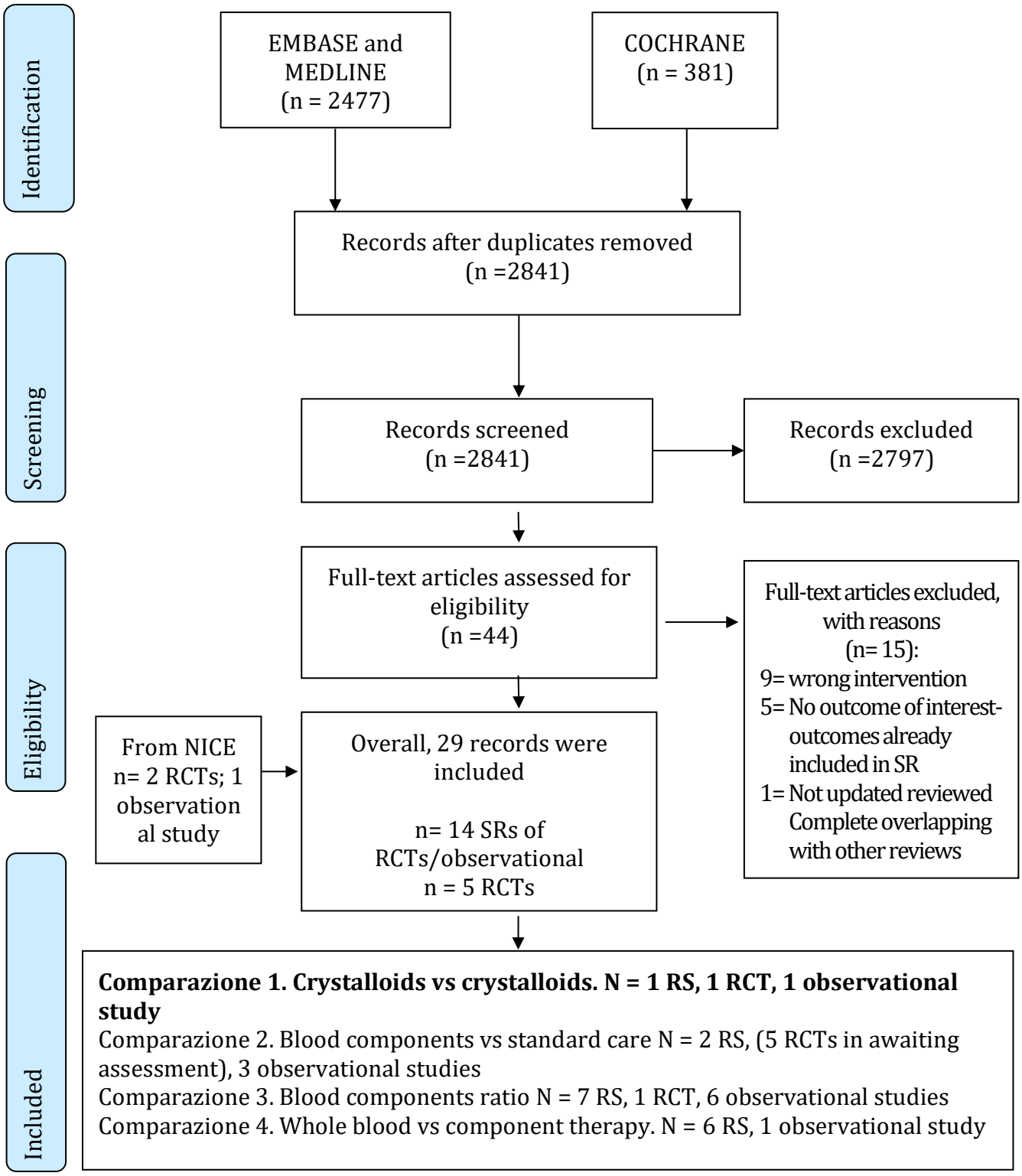
Appendici C1-C4 – Sintesi delle evidenze

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

Appendice C1 – Comparazione: crystalloids vs crystalloids

SELEZIONE DEGLI STUDI

Figure 1. Flow Chart of study selection



OUTCOME

E' stata effettutata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono state individuate una SR (Safieiko 2020), 1 studio randomizzato e controllato incluso dalla linea guida NCIE (Young 2016) e 1 studio osservazionale (Rowell 2016) che permettono di rispondere alla seguenti comparazioni includendo gli outcome critici e importanti:

1. Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normail saline/lactated Ringer's solution (LR)) (Safiejko 2020 – systematic review)
2. Normal saline versus lactated Ringer's solution (LR) (Rowell 2016 – observational study) – subgroup TBI
3. Plasma Lyte A versus normal saline (Young 2014 – randomized controlled trial)

Gli outcome riportati nella revisione e negli studio osservazionali sono riportati in tabella:

Author - year	Study design	Comparison	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological wellbeing)
Safiejko 2020	SR (15 trials)	1.Hypertonic saline/dextran or hypertonic saline versus isotonic fluid							
Rowell 2016	Observational study	2.Normal saline versus lactated Ringer's solution (LR) **Subgroup: *TBI patients***							
Young 2014	Randomized controlled trial	3.Plasma Lyte A versus normal saline							

Author - year	Study design	Mortality at 24 hours, 30 days/1month and 12 months	Quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes:
Hypertonic saline/dextran or hypertonic saline versus isotonic fluid								
Safiejko 2020	SR (15 trials)	***24 h survival*** Survival to hospital discharge rate 88.6% in hypertonic saline/dextran (HSD) group vs. 72.3% for isotonic fluid (NS) solutions (OR = 2.99; 95% CI 2.04–4.39; I2 = 0%; p = 0.09; 9 trials). ***Survival at discharge.*** Survival to hospital discharge rate 71.2% in hypertonic saline/dextran (HSD) group vs. 68.4% for isotonic fluid (NS) solutions (OR = 1.19; 95% CI 0.97–1.45; I2 = 48%; p = 0.09; 9 trials). Subgroup: • *hypertonic saline/dextran (HSD) vs isotonic fluid (NS) solutions*: OR 1.13 (95% CI 0.89 – 1.44, I2=36%, p=0.14; 8 trials); • *hypertonic saline vs isotonic fluid (NS) solutions:* OR 1.10 (95% CI 0.83 – 1.44, I2=0%, p=0.56; 4 trials) ***28- to 30-days survival rate.*** Pooled analysis showed that the use of hypertonic fluid solutions was 72.8% survivable, while in the case of isotonic fluid (NS) — 71.4% (OR = 1.13; 95% CI 0.75–1.70; I2 = 43%; p = 0.56; 5 trials). Subgroup: • *hypertonic saline/dextran (HSD) vs isotonic fluid (NS) solutions*: OR 1.06 (95% CI 0.64 – 1.77, I2=56%, p=0.08; 4 trials); • *hypertonic saline vs isotonic fluid (NS) solutions:* OR 1.14 (95% CI 0.71 – 1.83, I2=49%, p=0.16; 2 trials). **Overall mortality** Overall, OR 0.76 (95% IC 0.61 – 0.94). Subgroup: • *hypertonic saline/dextran (HSD) vs isotonic fluid (NS) solutions*: OR 0.72 (95% CI 0.55 – 0.94, I2=20%, p=0.28; 6 trials); • *hypertonic saline vs isotonic fluid (NS) solutions:* OR 0.90 (95% CI 0.66 – 1.23, I2=10%, p=0.33; 3 trials)	No outcome	The use of hypertonic fluid was associated with a longer hospital stay than with isotonic fluid solutions (mean difference [MD] = 1.45; 95% CI 0.43–2.46; p = 0.005).	Acute respiratory distress syndrome-free survival rate at 28 days. The difference between hypersaline and normosaline groups was not statistically significant (OR = 1.10; 95% CI 0.85–1.44; p = 0.46; 2 trials). See table below for more details.	No outcome	No outcome	No outcome

Normal saline versus lactated Ringer's solution (LR) Subgroup: TBI patients								
Rowell 2016	Observational study	In patients with AIS head ≥ 3, unadjusted 30-day mortality was 50% in the LR group and 28% in the NS group. Survival analysis of patients with AIS head ≥ 3 using a Cox proportional hazards model with random effects showed increased mortality in the LR group compared with the NS group at 30 days (HR 1.78, CI 1.04–3.04, p = 0.035).	No outcome	No outcome	No outcome	No outcome	No outcome	No outcome
Plasma Lyte A versus normal saline								
Young 2014	Randomized controlled trial	In-hospital mortality at 30 days 0R 0.8, CI 0.2 – 3.3	No outcome	0.9% NaCl (n = 24) days median IQR: 4 (2, 13) Plasma-Lyte (n = 22) days median IQR: 4 (1, 9)	There were no identifiable adverse events in either arm.	No outcome	No outcome	No outcome

1. *Mortality at 24 hours, 30days/1 month, and 12 months*

Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normal saline/lactated Ringer's solution (LR))

Safiejko 2020 (15 trials)

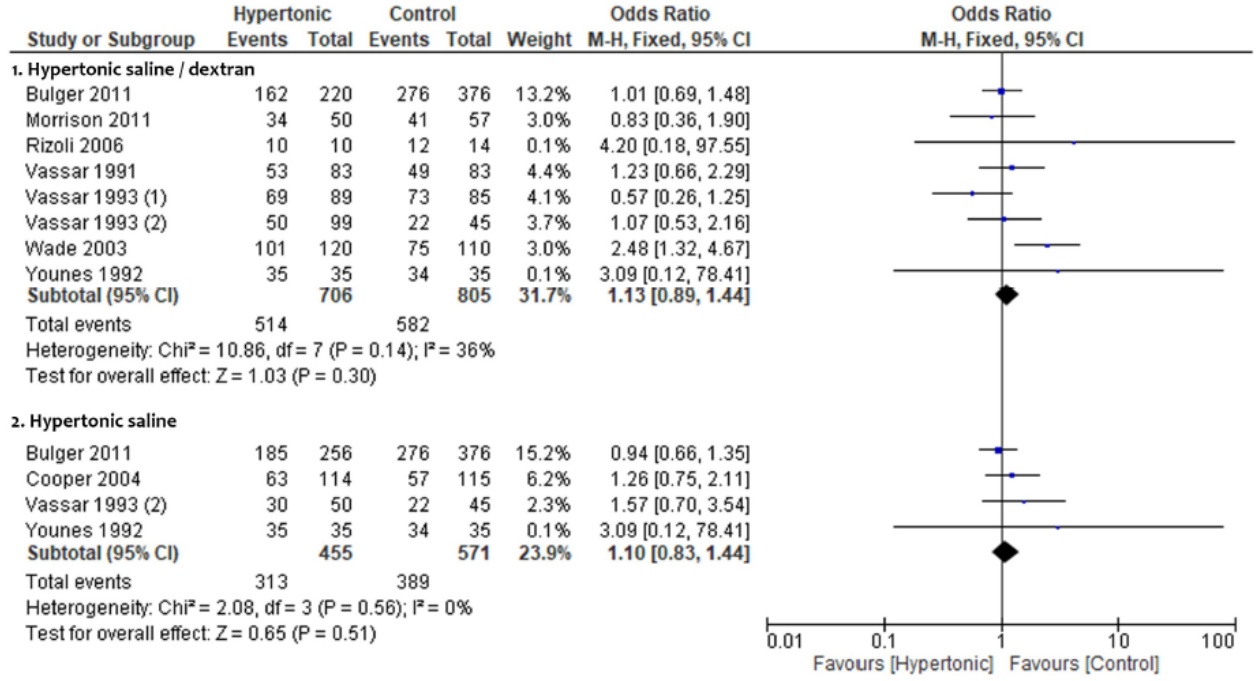


Figure 1. Forest plot of survival to hospital discharge rate while using hypertonic fluid solutions versus isotonic fluid solutions. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

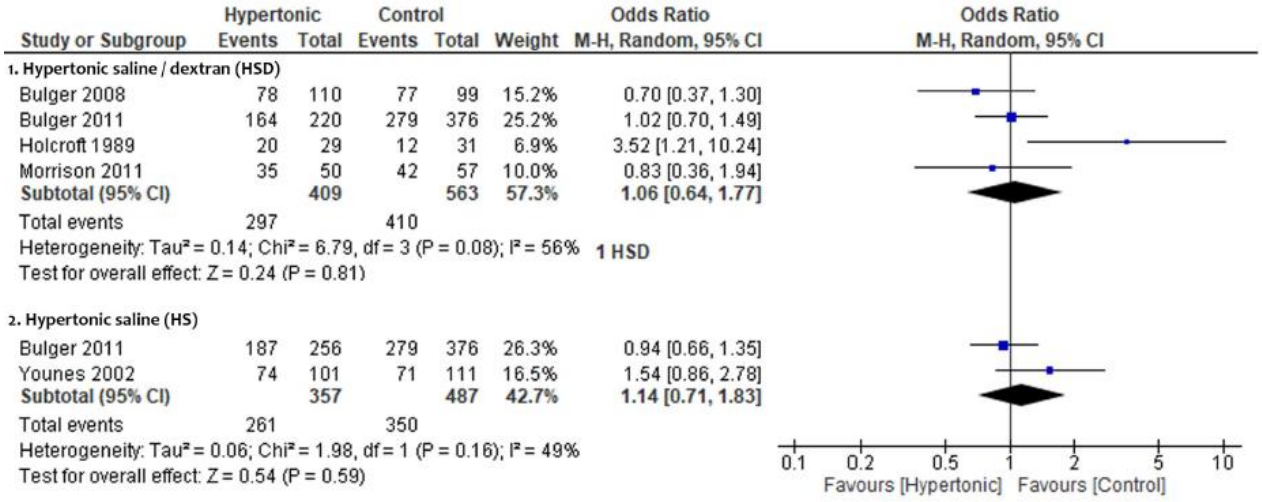


Figure 3. Forest plot of 28- to 30-days survival rate while using hypertonic fluid solutions versus isotonic fluid solutions. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

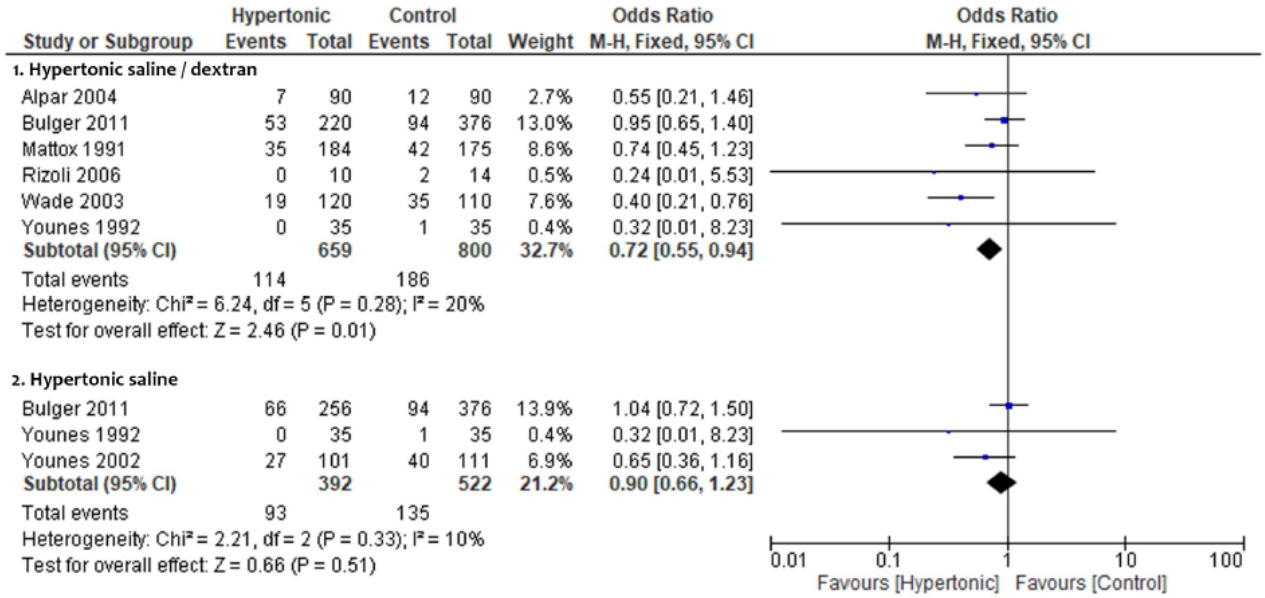


Figure 4. Forest plot of overall mortality rate while using hypertonic fluid solutions versus isotonic fluid solutions. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

Table 2. Characteristics of outcomes: hypertonic fluid solutions versus isotonic fluid solutions.

Type of adverse event	Number of trials	Total numer of patients	Percentage of adverse event		Treatment effect (hypertonic vs. normotonic fluid solutions) OR/MD (95% CI)	P value	I^2, statistic, %
			HSD or HS	NS			
24-h survival							
HSD	2	575	89.4%	73.8%	2.99 (1.88–4.75)	**< 0.001**	18%
NS	2	332	86.4%	68.6%	3.01 (1.54–5.89)	**0.001**	23%
Total	4	807	88.6%	72.3%	2.99 (2.04–4.39)	**< 0.001**	0%
28- to 30-day survival							
HSD	4	972	72.6%	72.8%	1.06 (0.64–1.77)	0.81	56%
NS	2	844	73.1%	71.9%	1.14 (0.71–1.83)	0.59	49%
Total	5	1440	72.8%	71.4%	1.13 (0.75–1.70)	0.56	54%
Survival to discharge							
HSD	8	1511	72.8%	72.3%	1.13 (0.89–1.44)	0.30	36%
NS	4	1026	68.8%	68.1%	1.10 (0.83–1.44)	0.51	0%
Total	9	2081	71.2%	69.4%	1.19 (0.97–1.45)	0.09	48%
Survival at 3 months							
HSD	–	–	–	–	–	–	–
NS	1	228	55.3%	48.2%	1.33 (0.79–2.23)	0.29	–
Total	1	228	55.3%	48.2%	1.33 (0.79–2.23)	0.29	–
Overall mortality							
HSD	6	1459	17.3%	23.3%	0.72 (0.55–0.94)	**0.01**	20%
NS	3	914	23.7%	25.9%	0.90 (0.66–1.23)	0.51	10%
Total	7	1962	19.7%	24.8%	0.76 (0.61–0.94)	**0.01**	33%

ARDS — acute respiratory distress syndrome; CI — confidence interval; HSD — hypertonic fluid solutions; MD — mean difference; NS — izotonic/norotonic fluid solutions; OR — odds ratio

Normal saline versus lactated Ringer's solution (LR) (subgroup TBI patients)

Lo studio osservazionale di Rowell 2016 include sottogruppi brain-injured (AIS head ≥ 3) and non-brain injured (AIS head ≤ 2) patients.

Gruppo 1. Brain-injured (AIS head ≥ 3)

In patients with AIS head ≥ 3, unadjusted 30-day mortality was 50% in the LR group and 28% in the NS group. Survival analysis of patients with AIS head ≥ using a Cox proportional hazards model with random effects showed increased mortality in the LR group compared with the NS group at 30 days (HR 1.78, CI 1.04–3.04, p = 0.035).

TABLE 3B. REPORTED CAUSES OF DEATH IN PATIENTS WITH AIS HEAD ≥3

Cause	*LR* (n=27)	*NS* (n=73)	P *value*
Exsanguination	9 (33.3%)	15 (20.5%)	0.197
Brain injury	19 (70.4%)	47 (64.4%)	0.641
Cardiovascular	10 (37.0%)	9 (12.3%)	0.009
Multiple organ failure	2 (7.4%)	8 (11.0%)	0.725
Airway/respiratory	6 (22.2%)	12 (16.4%)	0.561
Sepsis	0 (0%)	3 (4.1%)	0.561
Other causes	1 (3.7%)	6 (8.2%)	0.671

Percentages do not add to 100 because centers were allowed to list more than one cause of death.
LR, lactated Ringer's; NS, normal saline.

Gruppo 2. Non-brain injured (AIS head ≤ 2)
In patients with AIS head ≤ 2, unadjusted 30-day mortality was 25% in the LR group and 11% in the NS group. No difference in 30-day mortality was observed in patients with AIS head ≤2 (HR 1.49, CI 0.757–2.95, p = 0.247).
Comparison of the dominant LR center versus all other centers also revealed no difference in 30-day mortality using Cox regression modeling (HR 1.86, p = 0.890).

Plasma Lyte A versus normal saline

Tra le prove disponibili, uno studio randomizzato e controllato (Young 2014) condotto su pazienti adulti con trauma e necessità di trasfusione riporta l'outcome di interesse.

TABLE 3. Clinical Outcomes at 30 Days for Patients Receiving 0.9% NaCl Versus Plasma-Lyte

Outcome	**0.9% NaCl (n = 24)**	**Plasma-Lyte (n = 22)**	**Difference or RR (95% CI)**
Open abdomen within 30 days*	5 (21)	4 (18)	0.9 (0.3–2.8)
Open abdomen closed within 30 d*	4/5 (80)	3/4 (75)	0.9 (0.5–1.9)
Open abdomen-free days within 30 d†	25 ± 10	27 ± 7	1 (−4 to 6)
Ventilator-free days within 30 d†	20 ± 12	23 ± 10	2 (−4 to 9)
Maximum SOFA score within 30 d†	10 ± 7	9 ± 7	− 1 (−5 to 3)
Organ failure-free days within 30 d†	25 ± 11	26 ± 11	1 (−6 to 8)
ICU length of stay, d‡	4 (2, 13)	4 (1, 9)	—
Hospital length of stay, d‡	9 (4, 30)	12 (4, 21)	—
In-hospital mortality at 30 d*,§	4 (17)	3 (14)	0.8 (0.2–3.3)

*Number (%).
†Mean ± standard deviation.
‡Median (interquartile range).
§Modified intent-to-treat group.
CI indicates confidence interval; ICU, intensive care unit; RR, relative risk; SOFA, sequential organ failure assessment.

2. *Health related quality of life*

Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normail saline/lactated Ringer's solution (LR))

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Normal saline versus lactated Ringer's solution (LR) (subgroup TBI patients)

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Plasma Lyte A versus normal saline

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

3. *Length of intensive care stay*

Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normail saline/lactated Ringer's solution (LR))

Safiejko 2020

Type of adverse event	Number of trials	Total numer of patients	Percentage of adverse event		Treatment effect (hypertonic vs. normotonic fluid solutions) OR/MD (95% CI)	P value	I^2, statistic, %
			HSD or HS	NS			
Length of hospital stay (days)							
HSD	3	361	–	–	1.05 (–1.88–3.98)	0.48	0%
NS	1	222	–	–	1.50 (0.42–2.58)	**0.007**	–
Total	4	583	–	–	1.45 (0.43–2.46)	**0.005**	0%

Normal saline versus lactated Ringer's solution (LR) (subgroup TBI patients)

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Plasma Lyte A versus normal saline

Tra le prove disponibili, uno studio randomizzato e controllato (Young 2014) condotto su pazienti adulti con trauma e necessità di trasfusione riporta l'outcome di interesse.

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Open abdomen within 30 days*	5 (21)	4 (18)	0.9 (0.3–2.8)
Open abdomen closed within 30 d*	4/5 (80)	3/4 (75)	0.9 (0.5–1.9)
Open abdomen-free days within 30 d†	25 ± 10	27 ± 7	1 (−4 to 6)
Ventilator-free days within 30 d†	20 ± 12	23 ± 10	2 (−4 to 9)
Maximum SOFA score within 30 d†	10 ± 7	9 ± 7	− 1 (−5 to 3)
Organ failure-free days within 30 d†	25 ± 11	26 ± 11	1 (−6 to 8)
ICU length of stay, d‡	4 (2, 13)	4 (1, 9)	—
Hospital length of stay, d‡	9 (4, 30)	12 (4, 21)	—
In-hospital mortality at 30 d*,§	4 (17)	3 (14)	0.8 (0.2–3.3)

*Number (%).
†Mean ± standard deviation.
‡Median (interquartile range).
§Modified intent-to-treat group.
CI indicates confidence interval; ICU, intensive care unit; RR, relative risk; SOFA, sequential organ failure assessment.

4. *Adverse effects*

Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normail saline/lactated Ringer's solution (LR))

Safiejko 2020

Table 3. Characteristics of adverse events between hypertonic fluid solutions versus isotonic fluid solutions.

Type of adverse event	Number of trials	Total numer of patients	Percentage of adverse event		OR (95%CI)	P value	I^2, statistic, %
			HSD or HS	NS			
Nosocomial inections							
Pneumonia	4	1695	9.9%	9.8%	0.95 (0.68–1.31)	0.75	0%
ARDS	1	422	0.0%	0.9%	0.20 (0.01–4.15)	0.30	–
Blood stream infection	2	1061	7.2%	6.1%	1.18 (0.72–1.93)	0.51	0%
Urinary tract infection	2	1061	6.1%	7.6%	0.79 (0.49–1.28)	0.34	0%
Wound infection	2	1061	5.8%	4.0%	1.50 (0.84–2.67)	0.17	0%
Intra-abdominal abcess	2	631	1.6%	0.3%	3.49 (0.57–21.54)	0.18	11%
Sinustis	1	209	0.9%	0.0%	2.71 (0.11–67.69)	0.54	–
Pseudomembranous colitis	1	209	1.0%	0.0%	2.73 (0.11–67.69)	0.54	–
Line infection	1	209	1.0%	0.0%	2.73 (0.11–67.69)	0.54	–
Sepsis	1	422	0.0%	1.4%	0.14 (0.01–2.74)	0.20	–
Other	1	311	3.8%	0.0%	8.27 (0.47–144.75)	0.15	–
One or more nosocomial infections	2	1061	23.0%	21.9%	1.06 (0.79–1.42)	0.70	0%
Noninfectious complications							
Acute renal failure	3	780	0.8%	1.6%	0.52 (0.14–1.95)	0.33	0%
Abdominal compartment syndrome	1	209	3.6%	8.1%	0.43 (0.13–1.47)	0.18	–
Cardiac arrest	2	568	1.0%	1.5%	0.71 (0.17–2.88)	0.63	
Myocardial infarction	3	780	1.0%	2.1%	0.52 (0.16–1.67)	0.28	0%
Cerebral infarction	2	421	4.3%	2.8%	1.61 (0.58–4.53)	0.36	0%
Dead bowel	1	359	0.0%	0.6%	0.32 (0.01–7.79)	0.48	–
Deep vein thrombolysis	1	209	0.9%	7.0%	0.12 (0.01–1.00)	0.05	–
Pulmonary embolism	2	568	0.3%	1.1%	0.39 (0.06–2.70)	0.34	0%
Coagulopathy	1	359	0.9%	0.0%	2.73 (0.11–67.69)	0.54	–

ARDS — acute respiratory distress syndrome; CI — confidence interval; HS — hypertonic saline; HSD — hypertonic fluid solutions; NS — isotonic/norotonic fluid solutions; OR — odds ratio

Normal saline versus lactated Ringer's solution (LR) (subgroup TBI patients)

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Plasma Lyte A versus normal saline

Tra le prove disponibili, uno studio randomizzato e controllato (Young 2014) condotto su pazienti adulti con trauma e necessità di trasfusione riporta l'outcome di interesse.
"There were no identifiable adverse events in either arm. Per protocol,we discontinued study fluid for 1 subject secondary to hyperkalemia 12 hours postinjury. Subsequent unblinding of the treatment arms showed that this subject was in the 0.9% NaCl arm."

5. *Acute transfusion reaction*

Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normail saline/lactated Ringer's solution (LR))

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Normal saline versus lactated Ringer's solution (LR) (subgroup TBI patients)

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Plasma Lyte A versus normal saline

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

IMPORTANT OUTCOMES

6. ***Time to definitive control of haemorrhage***

Tra le prove di evidenza incluse, nessuna comparazione riporta l'outcome di interesse.

7. ***Patient-reported outcomes: pain/discomfort return to normal activities psychological wellbeing)***

Tra le prove di evidenza incluse, nessuna comparazione riporta l'outcome di interesse.

Safiejko 2020

Caratteristiche degli studi inclusi nella revisione di Safiejko 2020.

Table 1. Characteristics of included studies.

Study	Country	Study Design	Intervention	Hyper-saline group			Controll group		
				N	Age	Males	N	Age	Males
Alpar et al. 2004	UK	RCT	Patients randomized to receive HSD or Hartmann's. HSD infused at a dose of 4 mL/kg or maximum 250 mL, with further fluid resuscitation with Hartmann's or blood transfusion. Average volume infused: HSD group: 4.5 L, Hartmann's group: 6.5 L	90	34.3 ± 11.3	NS	90	33.5 ± 11	ns
Bulger et al. 2008	USA	Double-blind RCT	Prehospital resuscitation with 250 mL either HSD or Ringer's lactate. Additional ongoing resuscitation with Ringer's lactate only	110	41 ± 18	69 (62.7%)	99	38 ± 19	68 (68.7%)
Bulger et al. 2011	Multi-country	Multicenter double-blind RCT	Patients randomized to receive a 250-mL bolus of either 7.5% HS, 7.5% HSD 70 or NS, in prehospital setting	476	37.2 ± 16.7	375 (78.8%)	376	36.2 ± 16.4	291 (77.4%)
Cooper et al. 2004	Australia	Double-blind RCT	Patients randomized to receive a 250 mL bolus of either 7.5% saline or Ringer's lactate solution	114	38 ± 19	75 (65.8%)	115	37 ± 19	76 (66.1%)
Holcroft et al. 1987	USA	RCT	Patients randomized to receive a 3% NaCl (1028 mOsm/kg, 4 mL/kg) or lactated Ringer's solution (12 mL/kg)	10	36 ± 13	9 (90.0%)	10	36 ± 21	9 (90.0%)
Holcroft et al. 1989	USA	RCT	Patients randomized to receive a 3% NaCl (1028 mOsm/kg, 4 mL/kg) or lactated Ringer's solution (12 mL/kg)	29	38 ± 15.6	23 (79.3%)	31	38 ± 19	26 (83.9%)
Mattox et al. 1991	USA	Multicenter double-blind RCT	Patients randomized to receive 250 mL either HSD or Ringer's lactate as prehospital resuscitation	211	34 ± 12	184(87.2%)	211	33 ± 12	175 (82.9%)
Morrison et al. 2011	Canada	Randomized controlled feasibility trial	250 mL of NS or 250 mL of HSD in a single dose. If the paramedics failed to obtain an intravenous access, the study's solution could be started immediately at the arrival to the emergency department as long as this occurred within 4 h from the injury	50	46 ± 21	30 (60.0%)	57	43 ± 21	43 (75.4%)
Rizoli et al. 2006	Canada	Double-blind RCT	Patients randomized to receive a single 250-mL bolus of either HSD or normal saline. Mean (standard deviation) total volume in first 24 h; Control group: colloid 696 (773) mL, crystalloid 8080 (2736) mL; HSD group: colloid 361 (377) mL, crystalloid 7796 (3189) mL; p = 0.02 and p = 0.75 between groups for crystalloid and colloid respectively	10	49.3 ± 16.7	7 (70.0%)	14	47.5 ± 15.9	9 (64.3%)
Vassar et al. 1991	USA	Double-blind RCT	Trauma patient were given 250 mL of 7.5 HSD 70 or Ringer's lactate as prehospital resuscitation	83	30.3 ± 6.1	NS	83	32.3 ± 6.1	ns
Vassar et al. 1993 (1)	USA	Double-blind RCT	Trauma patients in prehospital transport were given 250 mL of: (1) normal saline; (2) 7.5% NaCl (HS); (3) 7.5% NaCl in 6% HSD 70	174	31.5 ± 14.5	NS	84	31 ± 12	ns
Vassar et al. 1993 (2)	USA	Double-blind RCT	Trauma patients were given 200 mL or more of: (1) Lactate Ringer's solution, (2) 7.5% hypertonic saline solution, (3) 7.5% HS combined with 6% HSD 70, (4) 7.5 HS combined with 12 HSD 70	149	32 ± 13	NS	45	37 ± 18	ns
Wade et al. 2003	USA	Double-blind RCT	Trauma patients were given 250 mL of HSD (7.5% NaCl/6% HSD 70) or 250 mL of normal saline (0.9% NaCl)	120	32 ± 10.4	NS	110	32 ± 10.5	ns
Younes et al. 1992	Brazil	Double-blind RCT	Emergency unit patients received either an intravenous bolus infusion of 250 mL of hypertonic/hypertonic 7.5% NaCl + 6% HSD 70 or an isotonic 0.9% NaCl (NS) solution	70	NS	NS	35	NS	ns
Younes et al. 2002	Brazil	Double-blind RCT	Emergency unit patients received either an intravenous bolus infusion of 250 mL of hypertonic/hypertonic 7.5% NaCl + 6% HSD 70 or an isotonic 0.9% NaCl (IS) solution	101	39.8 ± 11.2	93 (92.1%)	111	40.8 ± 12.2	92 (82.9%)

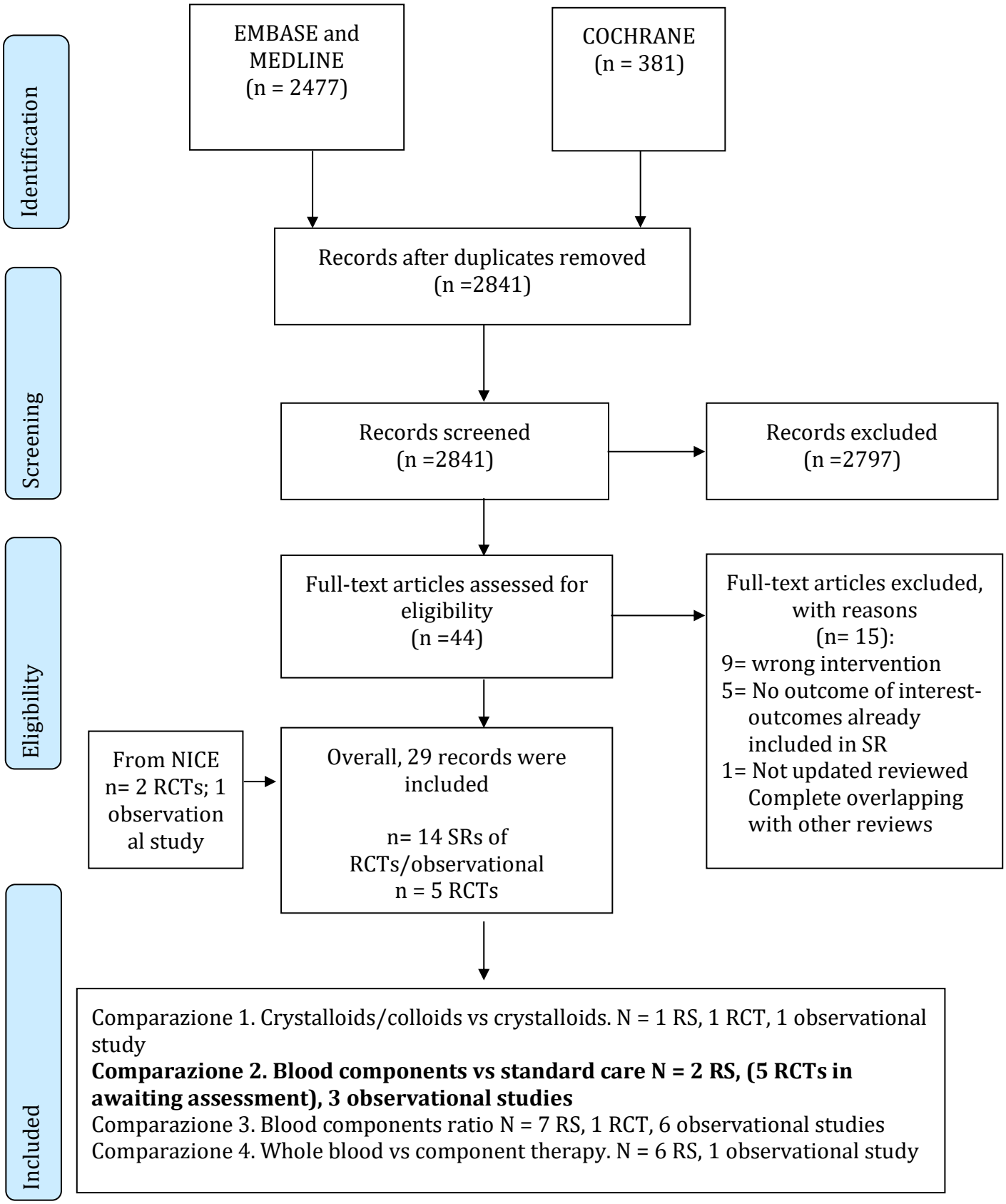
HS — hypertonic saline; HSD — hypertonic saline/dextran; NS — normotonic/isotonic fluid; ns — not specified; RCT — randomized controlled trial

Appendice C2 – Comparazione 2: Blood component therapy vs Standard care

INDICE

SELEZIONE DEGLI STUDI

Figure 1. Flow Chart of study selection



OUTCOME

E' stata effettutata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono stati valutati per elegibilità 2 RS, 5 RCT e 2 studi osservazionali.
In particolare i 5 RCT sono analisi secondarie del PAMPer Cluster Randomized Clinical Trial (Sperry 2018) e/o del COMBAT trial (Moore 2018) inclusi in entrambe le RS eligibili:

- Reitz 2020: Whether any beneficial effect of prehospital plasma varies across injury, blunt truama"
- Pusateri 2020 "We hypothesized that prehospital transport time influenced the effects of prehospital plasma on 28-day mortality."
- Gruen 2020, JAMA Network Open. "Association of Prehospital Plasma With Survival in Patients With Traumatic Brain Injury"
- Gruen 2020, Trauma Acute Care Surg "Characterization of unexpected survivors following a prehospital plasma randomized trial"
- Guyette 2019 "The aim of this study was to determine whether prehospital blood products reduce 30-day mortality in patients at risk for hemorrhagic shock compared with crystalloid only resuscitation."

Le 2 revisioni sistematiche identificate includono tutte analisi secondarie (per sottogruppi ed outcome di interesse). Tuttavia alcuni di questi analisi non sono finalizzate a dimostrare l'efficacia fra interventi pertanto i risultati vengono riportati in forma narrativa per completezza.
Sono state selezionate quindi 2 SRs che si sovrapponogono per PICO question e outcomes, entrambe con qualità molto bassa (Appendice D) e 3 studi osservazionali che permettono di indagare gli outcome critici e importanti rispondendo alla macro comparazione "Blood component therapy vs Standard care".
Per **Blood component therapy** si intende "prehospital blood-component transfusion (PHBT) defined as plasma and/or PRBCs and/or crystalloids".
Per **Standard care** si intende "infusion with crystalloids, no transfusion, unknown or combination with blood components."

La tabella 1 riporta i risultati delle due revisioni e degli studi osservazionali suddivisi per outcome e per le diverse comparazioni.

Table 1. Summary of Evidence

Author - year	Study design	Mortality at 24 hours, 30 days/1month and 12 months	Quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes:
PRBCs versus standard care								
Rijnhout 2019	SR	24 h:3 retrospective studies OR = 0.92; 95% CI, 0.46–1.85; P = 0.82 30 days: 4 retrospective studies OR = 1.18; 95% CI, 0.93–1.49; P = 0.17	No outcome	No outcome	In a total of 1341 patients who received PHBT, 14 adverse events were reported 1.04%, 95% CI 0.57–1.75%. However, not all included studies reported adverse events, which means that this number may be an underestimation of the actual number.	14 studies. Complication which was possibly related to the transfusion (1.04%, 95% CI 0.57–1.75%)	No outcome	No outcome
Grigg 2018	1 observational study	adjusted odds ratios (OR), after multiple imputation for both 6 h and 28 d mortality show no statistically significant association	No outcome	No outcome	No outcome	no immediate transfusion complications	No outcome	No outcome
PRBCs + plasma versus standard care								
Rijnhout 2019	SR	24 h:3 retrospective studies OR = 0.47; 95% CI, 0.29–0..83; I2=0 P = 0.008 30 days: 1 trials : OR = 0.51; 95% CI, 0.33–0.81; I2=0 P < 0.0001 3 retrospective studies: OR = 0.49; 95% CI, 0.23–0.83 P < 0.008	No outcome	1 trial: Moore 2018 Intensive-care-free day in plasma group: 23 (7 to 26), standard care: 24 (17 to 26), 0 (−3·00 to 1·00) p=0·49	1 trial: Sperry 2018: N°of patients with AEs: 2 in the standard care group (n=271) and 6 in the plasma group (n=230); N°of AEs: 4 in the standard care group (n=271) and 6 in the plasma group (n=230)	1 trial: Sperry 2018: 2 allergic reaction in the standard care group (n=271) and 0 in the plasma group (n=230)	No outcome	No outcome
Coccolini 2019	SR		No outcome				No outcome	No outcome

plasma versus standard care								
Rijnhout 2019	SR	1 trial: Moore 2018 More patients in the plasma group died than in the control group, but not significantly 24 h(p=0.68)and 1 month (p=0.37)	No outcome	1 trial: Moore 2018 Intensive-care-free day in plasma group: 23 (7 to 26), standard care: 24 (17 to 26), 0 (−3·00 to 1·00) p=0·49	1 trial: Sperry 2018 N°of patients with AEs: 2 in the standard care group (n=271) and 6 in the plasma group (n=230); N°of AEs: 4 in the standard care group (n=271) and 6 in the plasma group (n=230)	1 trial Sperry 2018: One transfusion-related or allergic reaction (0.4%) was reported in the standard-care group. 1 trial Sperry 2018: One transfusion-related or allergic reaction (0.4%) was reported in the standard-care group.	No outcome	No outcome
Coccolini 2019	SR	24 h: 2 trials, (RR = 0.69; 95% CI = 0.48–0.99) 1month: 2 trials, (RR = 0.86; 95% CI = 0.68–1.11)	No outcome				No outcome	No outcome
Packed red blood cells (PRBCs) + cryoprecipitate versus no cryoprecipitate								
Ditillo 2018	1 observational study	24h: OR, 0.78 [0.63–0.84], p = 0.02 in-hospital mortality: OR, 0.79 [0.77–0.87], p = 0.01	No outcome		in-hospital complications (OR, 1.48 [0.71–1.99], p = 0.31)		No outcome	No outcome
High C:PRBC versus Low C:PRBC								
Neal 2012	1 observational study	OR 0.9 (0.58 - 1.45)	No outcome		MOF: OR 1.7 (1.2-2.6) ARDS: OR2.2 (1.5-3.1)		No outcome	No outcome

MOF: Multi organ Failure; ARDS: Acute Respiratory Distress Syndrome

Tabella 2. Overlapping fra le SRs incluse per PICO questions and included studies.

All SRs have critically low quality.

	SR	Rijnhout 2019	Coccolini 2019
Number of studies and update searches		2 RCTs (Moore 2018, Sperry 2018) 7 retrospective studies, up to August 1st 2018	2 RCTs (Moore 2018, Sperry 2018) up to August 2018
Pico questions and characteristics	**Population**	trauma patients	Trauma patients with haemorrhagic shock
	Intervention and comparison	Prehospital blood-component transfusion (PHBT)	pre-hospital plasma vs. usual care
	Outcomes	For the primary outcomes (24-hour mortality and long-term mortality), metaanalysis was conducted. Twenty-four-hour mortality was defined as patients who died within 24 h after injury, including patients who died in the prehospital setting on scene or during transport. Long-term mortality was defined as 30-day or in-hospital mortality. Secondary outcome was adverse events resulting from PHBT.	The primary outcome measures for the meta-analysis were mortality at 24 h and at 1 month. Secondary outcome was morbidity (acute lung injury and multi-organ failure).
	language	The search was not restricted by language or publication status.	The search was not restricted by language or publication status.
	setting	Pre-hospital	Pre-hospital
	study design	randomized and retrospective studies: cohorts with matched patients	randomized trials

Gli studi identificati per la macro comparazione "Blood component therapy vs Standard care" permettono di rispondere alle seguenti comparazioni di interesse:

C1- Packed red blood cells (PRBCs) *versus* standard care (1 RS, 1 studio osservazionale)

C2-Packed red blood cells (PRBCs) + plasma *versus* standard care (1 RS)

C3-Plasma *versus* standard care (2 RS)

C4-Packed red blood cells (PRBCs) + cryoprecipitate *versus* no cryoprecipitate (1 osservazionale)

C5-High C:PRBC *versus* Low C:PRBC (1 osservazionale)

C6-Secondary analyses of the multicenter PAMPer and COMBAT trials (5 secondary analysis of RCT)

C1-Packed red blood cells (PRBCs) versus standard care

Author - year	Study design	Trials assessing the comparisons blood components vs standard care	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological wellbeing)
Rijnhout 2019	SR (quantitative synthesis)	4 observational							
Griggs 2018	single centre retrospective observational cohort study	1 observational							

Critical:

1. ***Mortality at 24 hours, 30 days/1month and 12 months***

Rijnhout 2019:SR

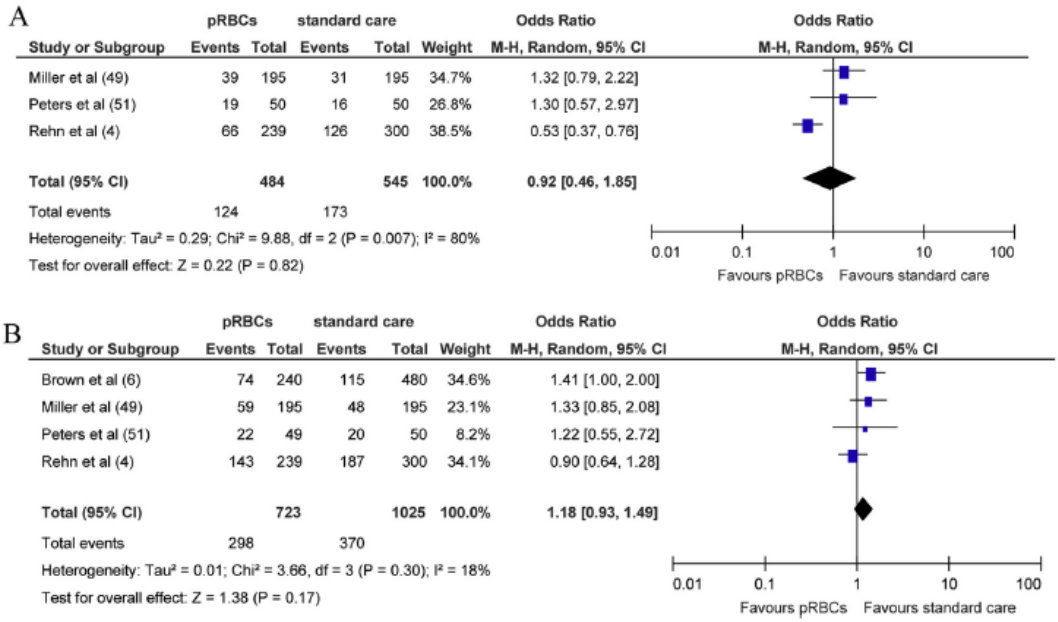


Fig. 2. (a) Comparison of prehospital transfusion with packed red cells only vs. standard care on 24-hour mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals. (b) Comparison of prehospital transfusion with packed red cells only vs. standard care on long-term mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals.

Effectiveness of pRBCs on 24-hour mortality

Three studies with matched civilian trauma patients reported 24-hour mortality [49,51,4]. A total of 484 civilian trauma patients received pRBCs, which were compared to 545 patients receiving only standard care. The total number of events in the pRBCs group was 124, compared to 173 in the control group. Pooled data showed no difference in 24-hour mortality (OR = 0.92; 95% CI, 0.46–1.85; P = 0.82; Fig. 2a). Study heterogeneity was high (I2 80%).

Effectiveness of pRBCs on long-term mortality

A total of four studies reported long-term mortality in patients who received PHBT with pRBCs only [6,51,49,4]. In total, 723 patients were transfused compared with 1025 patients receiving only standard care. All studies were performed in a civilian setting. The total number of events in the pRBCs group was 298, compared to 370 in the standard care group. Heterogeneity was low (I2 18%). Pooled data showed no difference in long-term mortality between the standard care and PHBT groups (OR = 1.18; 95% CI, 0.93–1.49; P = 0.17; Fig. 2b).

Griggs 2018: studio osservazionale

6 h and 28 days mortality:

Unadjusted analysis for observed 6 h mortality was less in the PRBC group (n = 10, 10%) versus the crystalloid group (n = 19, 18%) but not significantly so, p = 0.2. Similarly, for unadjusted 28 d mortality, there was an observed reduction in mortality in the PRBC group (n = 21, 26%) versus the crystalloid group (n = 31, 40%), p = 0.09. However, adjusted odds ratios (OR), after multiple imputation for both 6 h and 28 d mortality show no statistically significant association (Table 2).

Table 2 Odds ratios for 6 h and 28 d mortality (after multiple imputation adjusted for age, ISS, SBP, MOI)

Mortality	OR	Lower 95% CI	Upper 95% CI	*P* value
6 h	0.48	0.19	1.19	0.11
28 d	0.66	0.32	1.35	0.26

3. Length of intensive care stay

nessun dato

4. Adverse effects

Rijnhout 2019: SR
No separate assessment for PRBCs versus standard care.In a total of 1341 patients who received PHBT, 14 adverse events were reported 1.04%, 95% CI 0.57–1.75%. However, not all included studies reported adverse events, which means that this number may be an underestimation of the actual number.

5. Acute transfusion reaction

Rijnhout 2019: SR
In the studies reporting adverse events, a total of 1341 trauma patients were transfused, and 14 of them developed a complication which was possibly related to the transfusion (1.04%, 95% CI 0.57–1.75%). Complications were directly after admission an allergic reaction with rash (n = 5), a possible breathing depression (n = 1), anaphylaxis (n = 1), hypotension (n = 1) and urticaria (n = 1).
In 4 patients the authors could not conclude whether the complication was a direct result of the transfusion.
Griggs 2018: studio osservazionale
During the study period there were no immediate transfusion complications, and 100% traceability of pre-hospital PRBC was achieved

Important:

6. Time to definitive control of haemorrhage

nessun dato

7. Patient-reported outcomes: return to normal activities psychological wellbeing)

nessun dato

C2-Packed red blood cells (PRBCs) +plasma versus standard care

Author - year	Study design	Trials assessing the comparisons blood components vs standard care	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological
Rijnhout 2019	SR (quantitative synthesis)	3 observational + 1 RCT							

Rijnhout 2019

Study design	Author	intervento	controllo
rct	Sperry et al.	pRBCs +plasma	standard care
obs	Shackelford et al.	PHBT:38 patients pRBCs, 7 plasma only 10 PRBCs and plasma	standard care
obs	Holcomb etal	PHBT:plasma only (24%) pRBCs only(7%) Plasma +pRBCs (69%)	standard care
obs	O'Reilly et al.	PHBT:PRBCs1median [1,2] range[0-4] FFP 2median [1,2]	Standard care

Critical:

1. ***Mortality at 24 hours, 30 days/1month and 12 months***

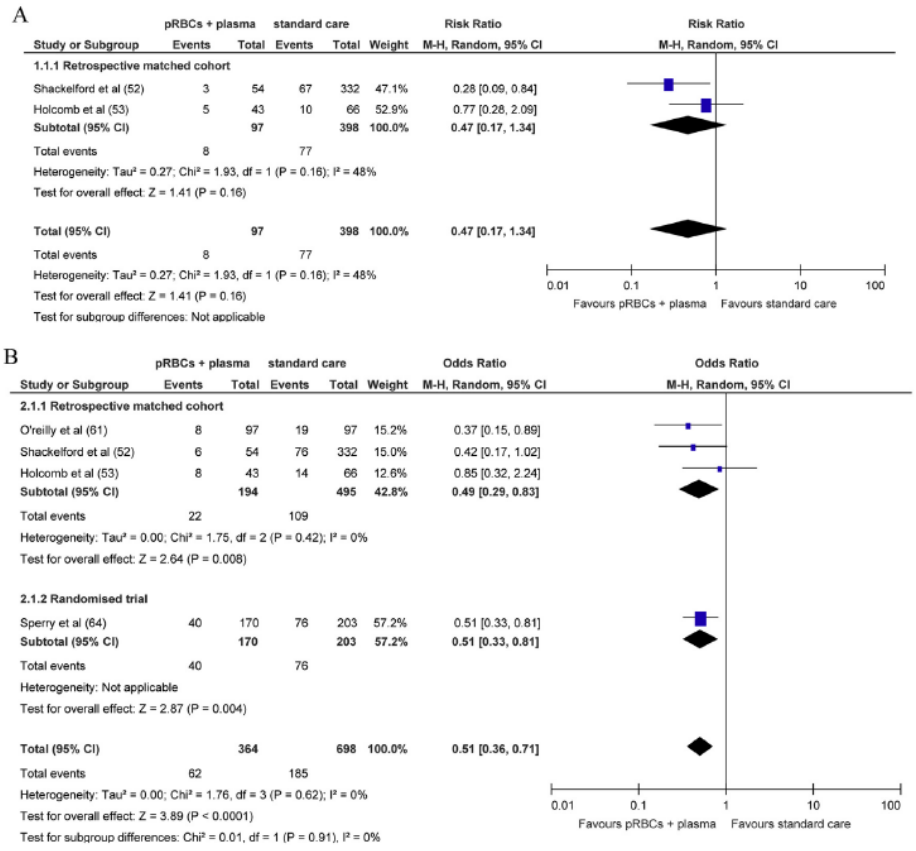


Fig. 3. (a) Comparison of prehospital transfusion with combined use of both packed red cells and plasma vs. standard care on 24-hour mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals.
(b) Comparison of prehospital transfusion with combined use of packed red cells and plasma vs. standard care on long-term mortality. The studies are shown by name with point estimates of the odds ratios and 95% confidence intervals.

Effectiveness of pRBCs and plasma on 24-hour mortality

Two retrospective studies with matched cohorts were included. One was performed in civilian [53] and one in military setting [52]. A total of 97 trauma patients received the combination of pRBCs and plasma compared with 398 matched control patients who only received standard care. The total number of events in the pRBCs and plasma group was 8, compared to 77 in the standard care group. Pooled data showed no difference in the odds for 24-hour mortality (OR = 0.47, 95% CI, 0.17–1.34; P = 0.16; Fig. 3a). Heterogeneity was defined as moderate (I2 48%).

Effectiveness of pRBCs and plasma on long-term mortality

Three retrospective studies and one RCT reported long-term mortality in patients who received combined transfusion with pRBCs and plasma [52,53,61,64]. Two studies were conducted in a civilian setting [53,64] and two studies in a military setting [52,61]. In total 364 patients received PHBT compared to 698 patients receiving only standard care. The total number of events in the intervention group was 62, compared to 185 in the standard care group. Heterogeneity was defined as low (I2 0%). Pooled data showed a 49% reduction in the odds for long-term mortality in the intervention group (OR = 0.51; 95% CI, 0.36–0.71; P < 0.0001) (Fig. 3b).

2. *Health related quality of life*

Nessun dato.

3. *Length of intensive care stay*

Nessun dato.

4. *Adverse effects*

Rijnhout 2019: SR
No separate assessment for PRBCs versus standard care.In a total of 1341 patients who received PHBT, 14 adverse events were reported 1.04%, 95% CI 0.57–1.75%. However, not all included studies reported adverse events, which means that this number may be an underestimation of the actual number.

5. *Acute transfusion reaction*

Rijnhout 2019: SR
In the studies reporting adverse events, a total of 1341 trauma patients were transfused, and 14 of them developed a complication which was possibly related to the transfusion (1.04%, 95% CI 0.57–1.75%). Complications were directly after admission an allergic reaction with rash (n = 5), a possible breathing depression (n = 1), anaphylaxis (n = 1), hypotension (n = 1) and urticaria (n = 1).
In 4 patients the authors could not conclude whether the complication was a direct result of the transfusion.

Important:

6. *Time to definitive control of haemorrhage*

Nessun dato.

7. *Patient-reported outcomes: return to normal activities psychological wellbeing)*

Nessun dato.

C3-Plasma verus standard care

Author - year	Study design	Trials assessing the comparisons blood components vs standard care	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of	Patient-reported outcomes: return to normal activities psychological

Rijnhout 2019	SR (quantitative synthesis)	1 RCT (Moore 2018)		
Coccolini 2019	SR (quantitative synthesis)	2 RCT (Moore 2018; Sperry 2018)		acute lung injury and multi-organ failure

Critical:

1. ***Mortality at 24 hours, 30 days/1month and 12 months***

La review di Rijnhout 2019 considera soltanto l'RCT di Moore 2018 con intervento plasma poiché l'intervento in Sperry viene classificao come "pRBCs +plasma". La review di Coccolini invece identifca 2 RCT (Moore 2018 e Sperry 2018) con intervento di plasma.

Coccolini 2019 (SR): 2 RCT, Moore 2018 (COMBAT trial) e Sperry 2018 (PAMPer trial)

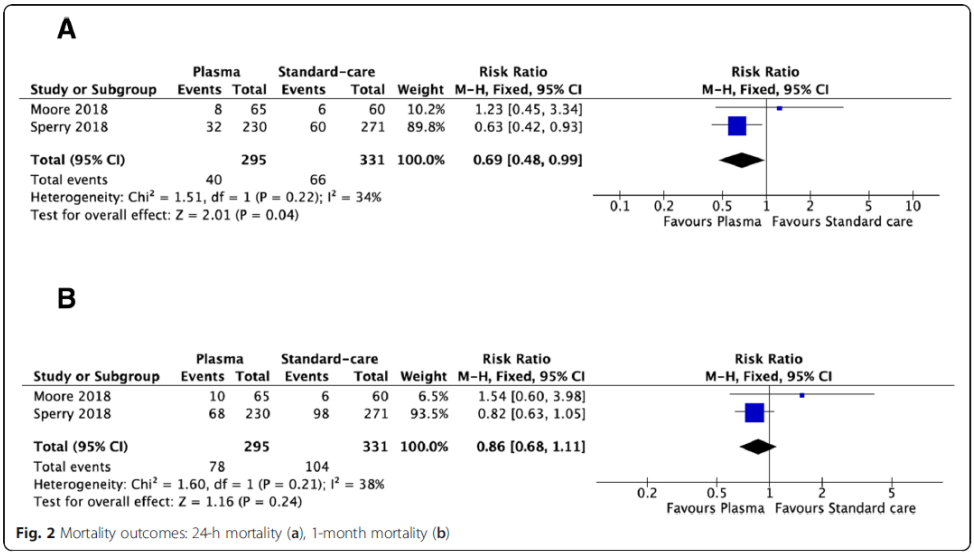


Fig. 2 Mortality outcomes: 24-h mortality (**a**), 1-month mortality (**b**)

Mortality at 24 h

Two hundred ninety-five patients received pre-hospital plasma and 331 usual care (Fig. 2). There was no statistical heterogeneity between studies. **In the fixed-effects model, the 24-h mortality was significantly higher in the standard treatment group** (RR = 0.69; 95% CI = 0.48–0.99).

Mortality at 1 month

Two hundred ninety-five patients received pre-hospital plasma and 331 usual care (Fig. 2). There was no statistical heterogeneity between studies. In the fixed-effects model**, the 1-month mortality was not significantly different between the two arms** (RR = 0.86; 95% CI = 0.68–1.11).

Moore 2018: COMBAT trial, incluso nella SR di Rijnhout 2019

Outcomes

	Plasma group (n=65)	Control group (n=60)	Effect size (95% CI)*	p value
Clinical outcome				
Mortality at 28 days†	10 (15%)	6 (10%)	1·54 (0·60 to 3·98)	0·37
Mortality at 24 h	8 (12%)	6 (10%)	1·23 (0·45 to 3·34)	0·68

Sperry 2018: PAMPer trial

Table 2. Secondary Trial Outcomes.*

Outcome	Standard-Care Group (N=271)	Plasma Group (N=230)	Difference (95% CI)†	Observed P Value‡	Adjusted P Value§
24-hr mortality — no. (%)	60 (22.1)	32 (13.9)	−8.2 (−14.9 to −1.6)	0.02	0.55
In-hospital mortality — no. (%)	88 (32.5)	51 (22.2)	−10.3 (−18.0 to −2.6)	0.01	0.33
Median total 24-hr volume of blood components transfused (IQR) — units	4 (2 to 16)	3 (0 to 10)		0.02	0.41
Median 24-hr volume of packed red cells transfused (IQR) — units	4 (1 to 9)	3 (0 to 7)		0.03	0.69
Median 24-hr volume of plasma transfused (IQR) — units	0 (0 to 4)	0 (0 to 3)		0.26	>0.99
Median platelet transfusion volume at 24 hours (IQR) — units	0 (0 to 1)	0 (0 to 1)		0.22	>0.99
Median 24-hr volume of crystalloids infused (IQR) — ml	4500 (3000 to 6800)	4388 (2225 to 6320)		0.14	>0.99
Vasopressors received in first 24 hr — no. (%)	138 (50.9)	104 (45.2)	−5.7 (−14.4 to 3.1)	0.21	>0.99
Multiorgan failure — no. (%)	156 (57.6)	145 (63.0)	5.4 (−3.1 to 14.1)	0.23	>0.99
Acute lung injury–acute respiratory distress syndrome — no. (%)	50 (18.5)	48 (20.9)	2.4 (−4.8 to 9.4)	0.50	>0.99
Nosocomial infection — no. (%)	49 (18.1)	46 (20.0)	1.9 (−4.9 to 8.8)	0.65	>0.99
Allergic reaction or transfusion-related reaction — no. (%)	1 (0.4)	5 (2.2)	1.8 (−0.2 to 3.8)	0.10	>0.99
Median initial prothrombin-time ratio (IQR)¶	1.3 (1.1 to 1.6)	1.2 (1.1 to 1.4)		<0.001	<0.001
Median initial results of rapid thromboelastography (IQR)‖					
Activated clotting time — sec**	113 (101 to 136)	113 (97 to 132)		0.39	>0.99
K-time — min††	1.9 (1.3 to 3.0)	1.8 (1.2 to 2.7)		0.17	>0.99
Alpha-angle — deg‡‡	68.3 (59.1 to 73.9)	70.6 (62.1 to 75.2)		0.08	>0.99
Maximal amplitude — mm§§	57.2 (48.6 to 63.2)	58.3 (49.1 to 63.6)		0.30	>0.99
LY30 — %¶¶	2.0 (0 to 30.0)	1.3 (0 to 20.0)		0.38	>0.99

* All transfusion and resuscitation volumes were totaled over the course of 24 hours beginning at the time of measurement of prehospital qualifying vital signs and enrollment; the 24-hour volumes of plasma transfused do not include the volume of plasma intervention.
† Differences are expressed as percentage points.
‡ Continuous variables were compared with the use of the Mann–Whitney U test, and categorical variables were compared with Fisher's exact test.
§ Significance levels were adjusted with the use of a Bonferroni correction to account for multiple comparisons. Adjusted P values were calculated by multiplying the observed P value by the number of comparisons (27 tests, which included all the secondary outcomes and subgroup interactions).
¶ Data were unavailable for 29 patients in the standard-care group and 24 patients in the plasma group.
‖ Thromboelastography was used to assess the viscoelastic properties of blood samples obtained during the trial.
** Activated clotting time is the time between the initiation of the test and the initial formation of fibrin and is longer when a patient has a clotting factor deficiency or severe hemodilution. Data were unavailable for 73 patients in the standard-care group and 66 patients in the plasma group.
†† K-time is the time that is needed to reach 20-mm clot strength and is generally longer when a patient has hypofibrinogenemia or a platelet deficiency. Data were unavailable for 72 patients in the standard-care group and 66 patients in the plasma group.
‡‡ Alpha-angle is the slope of the tracing that represents the rate of clot formation; the value decreases when a patient has hypofibrinogenemia or a platelet deficiency. Data were unavailable for 64 patients in the standard-care group and 60 patients in the plasma group.
§§ The maximal amplitude is the greatest amplitude of the tracing and reflects the contribution of platelets to clot strength. Data were unavailable for 63 patients in the standard-care group and 60 patients in the plasma group.
¶¶ LY30 is the percent reduction in amplitude 30 minutes after the maximal amplitude is reached; when elevated, it reflects a state of hyperfibrinolysis. Data were unavailable for 113 patients in the standard-care group and 98 patients in the plasma group.

2. *Health related quality of life*

Nessun dato.

3. *Length of intensive care stay*

Moore 2018: COMBAT trial, incluso nella SR di Rijnhout 2019

	Plasma group (n=65)	Control group (n=60)	Effect size (95% CI)*	p value
Clinical outcome				
Mortality at 28 days†	10 (15%)	6 (10%)	1·54 (0·60 to 3·98)	0·37
Mortality at 24 h	8 (12%)	6 (10%)	1·23 (0·45 to 3·34)	0·68
Acute lung injury within 28 days	28 (43%)	30 (50%)	0·86 (0·59 to 1·26)	0·44
Multiple organ failure within 28 days (Denver score >3)	4 (6%)	1 (2%)	3·69 (0·42 to 32·11)	0·37
Composite outcome (multiple organ failure or death) at 28 days‡	14 (21%)	7 (12%)	1·85 (0·80 to 4·26)	0·14
Ventilator-free days	26 (11 to 28)	26 (18 to 28)	0 (−1·00 to 0)	0·35
Intensive-care-free days	23 (7 to 26)	24 (17 to 26)	0 (−3·00 to 1·00)	0·49

4. Adverse effects

Sperry 2018: PAMPer trial

A total of 10 adverse events, which were defined as any events that were considered to be related to the trial regimen, were reported in the trial population; 3 of these were designated as serious adverse events (1 in the plasma group and 2 in the standard-care group) (Table 3).

Table 3. Adverse Events.*

Variable	Standard-Care Group (N=271)	Plasma Group (N=230)
No. of patients who had an adverse event	2	6
No. of adverse events	4	6
Adult respiratory distress syndrome	1†	0
Allergic reaction	0	2
Anaphylaxis	0	1
Fever	1	0
Hypotension	0	1
Pain	1	0
Sepsis	1†	0
Transfusion-related reaction	0	1†
Urticaria	0	1

* Adverse events were identified and reported at the discretion of the treating physician. Prospective definitions of adverse events are provided in Section XII of the protocol. An adverse event was defined as any adverse reaction that was considered to be related to the trial regimen. A serious adverse event was defined as any adverse reaction that was fatal or life-threatening, resulted in prolongation of hospitalization, or resulted in persistent or clinically significant disability or incapacity. The severity of adverse events was assessed by the site investigator. Potential allergic reactions and transfusion-related reactions were independently evaluated by personnel at blood bank services and by site investigators.

† This event was reported as a serious adverse event by the site investigator.

Coccolini 2019: SR with 2 RCTs

Of note, none of the studies reported any incidence of adverse events related to the transfusion of blood product on the field of the crush and failed to show an increase of transfusion-associated morbidities (i.e. acute lung injury and multi-organ failure). Moreover, pre-hospital plasma has no negative effects on multiple organ failure and acute lung injury.

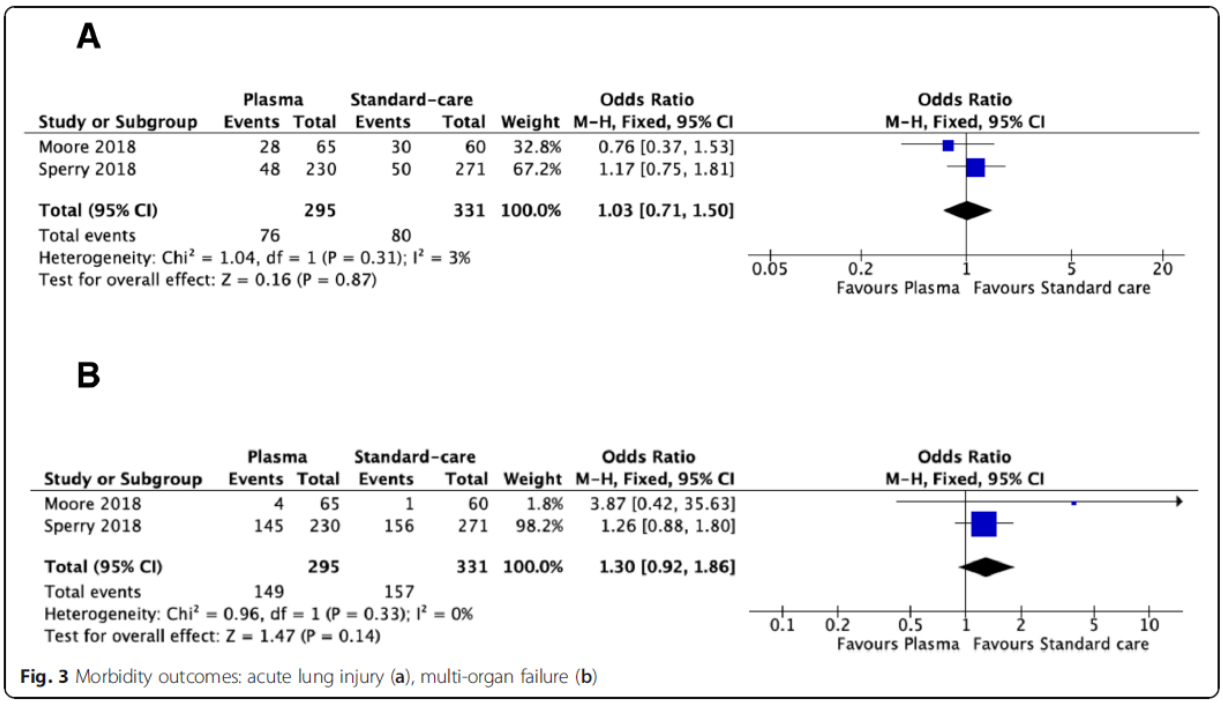


Fig. 3 Morbidity outcomes: acute lung injury (**a**), multi-organ failure (**b**)

1. ***Acute transfusion reaction***

Sperry 2018: PAMPer RCT

The management of each such reaction occurred during transport or at the time of arrival at the trauma center without further complication. One transfusion- related or allergic reaction (0.4%) was reported in the standard-care group.

Important:

2. ***Time to definitive control of haemorrhage***

Nessun dato.

3. ***Patient-reported outcomes: return to normal activities psychological wellbeing)***

Nessun dato.

C4-Packed red blood cells (PRBCs) + cryoprecipitate verus no cryoprecipitate

Author - year	Study design	Trials assessing the comparisons blood components vs standard care	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological wellbeing)
Ditillo 2020	Observational study								

The aim of study was to assess the role of cryoprecipitate as an adjunct to transfusion in trauma patients.

Critical:

1. ***Mortality at 24 hours, 30 days/1month and 12 months***

Ditillo 2020: observational study

The adjunctive use of cryoprecipitate in hemorrhaging trauma patients may reduce mortality. On multivariate logistic regression analysis, the use of cryoprecipitate as an adjunct to massive transfusion was associated with decreased 24-hour mortality (OR, 0.78 [0.63–0.84], p = 0.02), in-hospital mortality (OR, 0.79 [0.77–0.87], p = 0.01), but had no association with in-hospital complications (OR, 1.48 [0.71–1.99], p = 0.31) (Table 3).

TABLE 2. Univariate Analysis of Outcomes

Variables	Cryoprecipitate (n = 4,945)	No Cryoprecipitate (n = 14,698)	*p*
	24-h Transfusion, units, median [IQR]		
pRBCs	16 [10–27]	20 [14–31]	<0.01
Plasma	11 [6–19]	15 [10–23]	<0.01
Platelets	3 [2–5]	3 [1–4]	0.22
Whole blood	1 [1–1]	1 [1–1]	0.77
In-hospital complications, n (%)*	1,038 (50)	3,673 (49)	0.36
24 h mortality, n (%)	1,186 (24)	4,556 (31)	<0.01
In-hospital mortality, n (%)	2,077 (42)	7,202 (49)	<0.01

* Reported among those who survived their hospitalization.

TABLE 3. Multivariable Logistic Regression Analysis: Effect of Cryoprecipitate

Outcome	AOR	95% CI	*p*
24-h Mortality*	0.78	0.63–0.84	0.02
In-hospital mortality**	0.79	0.77–0.87	0.01
In-hospital complications†	1.48	0.71–1.99	0.31

*Hosmer-Lemeshow goodness-of-fit test: $p = 0.271$; AUROC = 0.761 [0.735–0.790].
**Hosmer-Lemeshow goodness-of-fit test: $p = 0.638$; AUROC = 0.759 [0.712–0.783].
†Hosmer-Lemeshow goodness-of-fit test: $p = 0.192$; AUROC = 0.732 [0.709–0.767].
AOR, adjusted odds ratio; CI, confidence interval.

2. *Health related quality of life*

Nessun dato.

3. *Length of intensive care stay*

Nessun dato.

4. *Adverse effects*

Ditillo 2020: observational study
The adjunctive use of cryoprecipitate in hemorrhaging trauma patients may reduce mortality without affecting in-hospital complications and transfusion requirements.
There was no difference between the two groups regarding complications (50% vs. 49%; p = 0.36)
or volume of platelet transfused (3 [2–5] vs. 3 [1–4]; p = 0.22) (Table 2). On multivariate logistic regression analysis, the use of cryoprecipitate as an adjunct tomassive transfusion was associated with decreased 24-hour mortality (OR, 0.78 [0.63–0.84], p = 0.02), in-hospital mortality (OR, 0.79 [0.77–0.87], p = 0.01), but had no association with in-hospital complications (OR, 1.48 [0.71–1.99], p = 0.31) (Table 3).

TABLE 2. Univariate Analysis of Outcomes

Variables	Cryoprecipitate (n = 4,945)	No Cryoprecipitate (n = 14,698)	*p*
	24-h Transfusion, units, median [IQR]		
pRBCs	16 [10–27]	20 [14–31]	<0.01
Plasma	11 [6–19]	15 [10–23]	<0.01
Platelets	3 [2–5]	3 [1–4]	0.22
Whole blood	1 [1–1]	1 [1–1]	0.77
In-hospital complications, n (%)*	1,038 (50)	3,673 (49)	0.36
24 h mortality, n (%)	1,186 (24)	4,556 (31)	<0.01
In-hospital mortality, n (%)	2,077 (42)	7,202 (49)	<0.01

* Reported among those who survived their hospitalization.

TABLE 3. Multivariable Logistic Regression Analysis: Effect of Cryoprecipitate

Outcome	AOR	95% CI	*p*
24-h Mortality*	0.78	0.63–0.84	0.02
In-hospital mortality**	0.79	0.77–0.87	0.01
In-hospital complications†	1.48	0.71–1.99	0.31

*Hosmer-Lemeshow goodness-of-fit test: $p = 0.271$; AUROC = 0.761 [0.735–0.790].
**Hosmer-Lemeshow goodness-of-fit test: $p = 0.638$; AUROC = 0.759 [0.712–0.783].
†Hosmer-Lemeshow goodness-of-fit test: $p = 0.192$; AUROC = 0.732 [0.709–0.767].
AOR, adjusted odds ratio; CI, confidence interval.

5. *Acute transfusion reaction*

Nessun dato.

Important:

6. Time to definitive control of haemorrhage

Nessun dato.

7. Patient-reported outcomes: return to normal activities psychological wellbeing)

Nessun dato.

C5-High C:PRBC vs Low C:PRBC

Author - year	Study design	Trials assessing the comparisons blood components vs standard care	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological wellbeing)
Neal 2012	RCT					MOF, ARDS			

AIM: to assess if an increased crystalloid: PRBC (C:PRBC) ratio would be associated with increased morbidity and poor outcome after MT.

Study	Intervention/comparison	Population	Outcomes	Comments
Neal 2012[102,103]	Crystalloid: pRBC ratio: <0.5:1 n=114	Patients receiving massive	Mortality (in-hospital)	Patients who died in the initial
	≥0.5:1 and <1.1 n=113 ≥1.1 and <1.5:1 n=111 ≥1.5:1 n=114	transfusion (≥10 units pRBC within the first 24 hours of admission). Blunt trauma only. Excluded patients <16 and >90 years. Mean age 42 years. USA	Nosocomial infection Multiple organ failure Acute respiratory distress syndrome	24 hours post injury were excluded. Analysis adjusted for age, gender, GCS, injury and shock severity, transfusion and resuscitation requirements, operative interventions and comorbidities. The effect of including FFP:pRBC ratio in the regression analysis for multiple organ failure and acute respiratory distress syndrome (note: not mortality). This had no effect on the results attributable to crystalloid: pRBC ratio >1/5:1

Critical:

8. Mortality at 24 hours, 30 days/1month and 12 months

Multivariate logistic regression revealed no significant association for the C:PRBC ratio with in-hospital mortality or the development of nosocomial infection (NI) (mortality: odds ratio [OR], 0.9; 95% confidence interval [CI], 0.58 –1.45; p =0.716 and NI: OR, 1.3; 95% CI, 0.68 –2.5; p = 0.408). However, after controlling for differences in age, gender, Glasgow Coma Scale, injury and shock severity, transfusion and resuscitation requirements, operative interventions, and comorbidities, the C:PRBC ratio was significantly associated with an independent higher risk of MOF (OR, 1.7; 95% CI, 1.2–2.6; p=0.008), ARDS (OR, 2.2; 95% CI, 1.5–3.1; p= 0.001), and ACS (OR, 2.3; 95% CI, 1.4 –3.8; p = 0.001).

9. Health related quality of life

Nessun dato.

10. Length of intensive care stay

Nessun dato.

11. Adverse effects

Logistic regression revealed that the 24-hour C:PRBC ratio was significantly associated with a greater independent risk of multiple organ failure (MOF), acute respiratory distress syndrome (ARDS), and abdominal compartment syndrome (ACS).

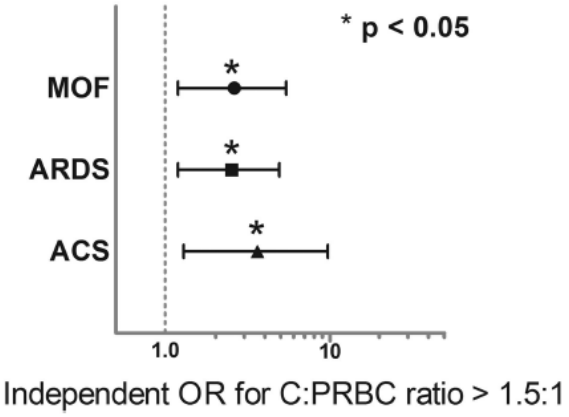


Figure 1. Independent ORs associated with infusion of crystalloid in a ratio >1.5:1 relative to PRBCs and the development of MOF, ARDS, and ACS.

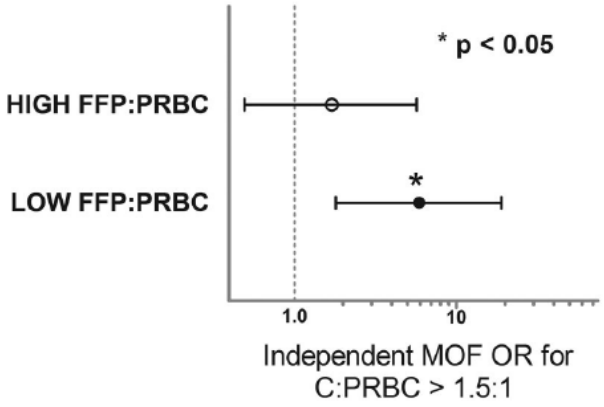


Figure 3. Independent ORs associated with infusion of crystalloid in a ratio >1.5:1 relative to PRBCs and the development of MOF stratified high and low FFP:PRBC ratios.

12. Acute transfusion reaction

Nessun dato.

Important:

13. Time to definitive control of haemorrhage

Nessun dato.

14. Patient-reported outcomes: return to normal activities psychological wellbeing)

Nessun dato.

C6-Secondary analyses of the multicenter PAMPer and COMBAT trials

1) Guyette 2019

Mortality 30 days

Four hundred seven patients were included. Patients receiving prehospital PRBC+plasma had the greatest mortality benefit. Crystalloid only had the worst survival.

TABLE 3. Cox Proportional Hazard Regression Treatment Effect Estimates by Prehospital Resuscitation Group for 30-day Mortality

	HR	95% CI	*P*
Crystalloid only	Reference	—	—
PRBC	0.68	0.49–0.95	0.025
Plasma	0.57	0.36–0.91	0.017
PRBC+Plasma	0.38	0.26–0.55	<0.001

95% CI indicates 95% confidence interval; HR, hazard ratio; PRBC, packed red blood cells.

PRBC + plasma had the greatest benefit [hazard ratio (HR) 0.38; 95% confidence interval (95% CI) 0.26–0.55, P<0.001], followed by plasma (HR 0.57; 95% CI 0.36–0.91, P=0.017) and PRBC (HR 0.68; 95% CI 0.49–0.95, P= 0.025) versus crystalloid only. Mortality was lower per-unit of PRBC (HR 0.69; 95% CI 0.52–0.92, p=0.009) and plasma (HR 0.68; 95% CI 0.54–0.88, P =0.003).

Crystalloid volume was associated with increased mortality among patients receiving blood products (HR 1.65; 95% CI 1.17–2.32, P= 0.004).

2) Pusateri 2019

OBJECTIVE To facilitate a post hoc combined analysis of the COMBAT and PAMPer trials to examine questions that could not be answered by either clinical trial alone.We hypothesized that prehospital transport time influenced the effects of prehospital plasma on 28-day mortality.

In this post hoc analysis of 626 patients (467 men [74.6%] and 159 women [25.4%]; median [interquartile range] age, 42 [27-57] years) who had trauma with hemorrhagic shock, a Cox regression analysis showed a significant overall survival benefit for plasma (hazard ratio [HR], 0.65; 95%CI, 0.47-0.90; P = .01) after adjustment for injury severity, age, and clinical trial cohort (COMBAT or PAMPer). A significant association with prehospital transport time was detected (from arrival on scene to arrival at the trauma center). Increased mortality was observed in patients in the standard care group when prehospital transport was longer than 20 minutes (HR, 2.12; 95%CI, 1.05-4.30; P = .04), while increased mortality was not observed in patients in the prehospital plasma group (HR, 0.78; 95%CI, 0.40-1.51; P = .46). No serious adverse events were associated with prehospital plasma transfusion.

Table 3. Rate and Likelihood of 28-Day and 24-Hour Mortality

	Mortality							
	28 d				24 h			
Model	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Unadjusted								
Treatment								
Plasma vs SC group[a]	0.69 (0.50-0.95)	.02	0.65 (0.45-0.94)	.02	0.66 (0.44-0.97)	.04	0.64 (0.42-0.99)	.04
Transport time from AOS to ED								
>20 vs ≤20 min								
Overall[b]	1.24 (0.77-1.98)	.38	1.30 (0.76-2.21)	.33	1.11 (0.64-1.91)	.72	1.12 (0.62-2.03)	.71
SC group[c]	2.00 (1.01-3.98)	.05	2.24 (1.05-4.78)	.04	2.08 (0.90-4.81)	.09	2.23 (0.91-5.47)	.08
Plasma group[d]	0.70 (0.37-1.35)	.29	0.69 (0.32-1.46)	.33	0.54 (0.26-1.14)	.11	0.51 (0.22-1.16)	.11
≤20 min								
Plasma vs SC group	1.68 (0.70-4.06)	.25	1.77 (0.66-4.79)	.26	2.04 (0.73-5.73)	.18	2.18 (0.71-6.71)	.17
>20 min								
Plasma vs SC group	0.60 (0.42-0.85)	.004	0.55 (0.37-0.81)	.003	0.54 (0.35-0.83)	.005	0.50 (0.31-0.80)	.004
Adjusted								
Model 1: overall[e]								
Plasma vs SC group	0.65 (0.47-0.90)	.01	0.60 (0.40-0.88)	.01	0.62 (0.42-0.93)	.02	0.58 (0.37-0.90)	.02
Model 2: overall[f]								
>20 vs ≤20 min	1.37 (0.85-2.21)	.20	1.54 (0.86-2.73)	.15	1.25 (0.71-2.22)	.45	1.33 (0.70-2.51)	.38
Model 3: SC treatment[g]								
>20 vs ≤20 min	2.12 (1.05-4.30)	.04	2.67 (1.16-6.16)	.02	2.14 (0.91-5.04)	.08	2.51 (0.97-6.48)	.06
Model 4: plasma treatment[g]								
>20 vs ≤20 min	0.78 (0.40-1.51)	.46	0.78 (0.35-1.75)	.55	0.68 (0.31-1.50)	.34	0.64 (0.27-1.56)	.33
Model 5: transport time ≤20 min[h]								
Plasma vs SC group	1.71 (0.70-4.16)	.24	1.94 (0.64-5.93)	.24	1.89 (0.65-5.40)	.25	2.44 (0.67-8.87)	.18
Model 6: transport time >20 min[h]								
Plasma vs SC group	0.56 (0.40-0.80)	.001	0.49 (0.33-0.75)	.001	0.53 (0.34-0.82)	.004	0.48 (0.29-0.77)	.003

Abbreviations: AOS, arrival on scene; ED, emergency department; HR, hazard ratio; OR, odds ratio; SC, standard care.

[a] Plasma group (n = 297) vs SC group (n = 329).

[b] More than 20 minutes (n = 530) vs 20 minutes or less (n = 96).

[c] More than 20 minutes (n = 275) vs 20 minutes or less (n = 54).

[d] More than 20 minutes (n = 255) vs 20 minutes or less (n = 42).

[e] Model 1 was adjusted for cohort, age, and injury severity score (ISS).

[f] Model 2 was adjusted for treatment, age, and ISS.

[g] Models 3 and 4 comprised analyses of treatment groups (SC or plasma) adjusted for age and ISS.

[h] Models 5 and 6 comprised stratification analyses of transport times (≤20 or >20 minutes) adjusted for age and ISS.

3) Reitz 2020

Aim: whether any beneficial effect of prehospital plasma varies across injury mechanism remains unknown.

We performed a secondary analysis using a harmonized dataset derived from two recent prehospital plasma randomized trials.

Blunt patients had higher injury severity, were older and had a lower GCS. Arrival indices of shock and coagulation parameters were similar across blunt and penetrating injury. The percentage of patients with a prehospital time less than 20 mins was significantly higher for penetrating patients relative to blunt injured patients (28.0% vs 11.6%, p<0.01). Stratified Kaplan-Meier curves demonstrated a significant separation for blunt injured patients (n=465, p=0.01) with no separation demonstrated for penetrating injured patients (n=161, p=0.60) Stratified Cox hazard regression verified, after controlling for all important confounders, that prehospital plasma was associated with a 32% lower independent hazard for 28 day mortality in blunt injured patients (HR 0.68, 95% CI 0.47–0.96, p= 0.03) with no independent survival benefit found in penetrating patients (HR 1.16, 95%CI 0.4–3.1,p=0.78).

Table 4.

Multivariate Cox-hazard regression model in blunt injured patients for 24-hour and 28-day mortality

	HR	95% CI	p-value
Blunt 24-hour			
Plasma (vs. standard care)	**0.59**	**0.370 – 0.947**	**0.029**
Age	1.01	0.999 – 1.023	0.074
ISS	1.00	0.987 – 1.019	0.751
Initial GCS	0.77	0.700 – 0.837	<0.001
PAMPer (vs. COMBAT)	1.29	0.627 – 5.137	0.276
Blunt 28-day			
Plasma (vs. standard care)	**0.68**	**0.472 – 0.965**	**0.031**
Age	1.02	1.007 – 1.029	0.001
ISS	1.02	1.001 – 1.029	0.031
Initial GCS	0.84	0.801 – 0.883	<0.001
PAMPer (vs. COMBAT)	2.35	0.980 – 5.628	0.055

4) Gruen JAMA Network Open 2020

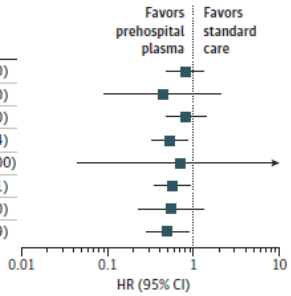
OBJECTIVE To assess the association between prehospital plasma and survival in patients with TBI.

In total, 166 patients had TBI (median [interquartile range] age, 43.00 [25.00-59.75] years; 125 men [75.3%]). When compared with the 92 patients who received standard care, the 74 patients with TBI who received prehospital plasma had improved 30-day survival even after adjustment for multiple confounders and assessment of the degree of brain injury with clinical variables and biomarkers (hazard ratio [HR], 0.55; 95%CI, 0.33-0.94; P = .03). Receipt of prehospital plasma was associated with improved survival among patients with TBI with a prehospital Glasgow Coma Scale score of less than 8 (HR, 0.56; 95%CI, 0.35-0.91) and those with polytrauma (HR, 0.50; 95%CI, 0.28-0.89). Patients with TBI transported

from the scene of injury had improved survival following prehospital plasma administration (HR, 0.45; 95%CI, 0.26-0.80; P = .005), whereas patients who were transferred from an outside hospital showed no difference in survival for the plasma intervention (HR, 1.00; 95%CI, 0.33-3.00; P = .99).

Figure 3. Hazard Ratios (HRs) for Each Subgroup Derived From a Cox Proportional Hazard Model

Source	No. of patients: Standard care	No. of patients: Prehospital plasma	HR (95% CI)
No TBI	179	156	0.80 (0.49-1.30)
Nonhead AIS <3	54	33	0.44 (0.09-2.10)
Nonhead AIS ≥3	123	120	0.82 (0.48-1.40)
TBI	92	74	0.52 (0.33-0.84)
GCS ≥8	17	22	0.70 (0.04-11.00)
GCS <8	72	52	0.56 (0.35-0.91)
Nonhead AIS <3	28	18	0.55 (0.23-1.30)
Nonhead AIS ≥3	63	53	0.50 (0.28-0.89)



HRs are reported for prehospital plasma compared with standard care. HRs less than or equal to 1 indicate a decreased risk of death; HRs greater than 1 indicate an increased risk of death. Traumatic brain injury (TBI) with mild to moderate traumatic injury in other body regions is defined by the presence of TBI and Abbreviated Injury Severity (AIS) score less than 3 in nonhead AIS categories (abdomen, chest, and extremity). Polytrauma with TBI is defined by the presence of TBI and AIS score of 3 or higher in the abdomen, chest, or extremity categories. GCS indicates Glasgow Coma Scale.

5) Gruen J Trauma Acute Care Surg 2020

We sought to characterize the unexpected survivors, patients who survived despite having high predicted mortality after traumatic injury.

METHODS: The PrehospitalAirMedical Plasma trial randomized severely injured patients (n = 501) to receive either standard care (crystalloid).

or two units of prehospital plasma followed by standard care fluid resuscitation. We built a generalized linear model to estimate patient mortality.

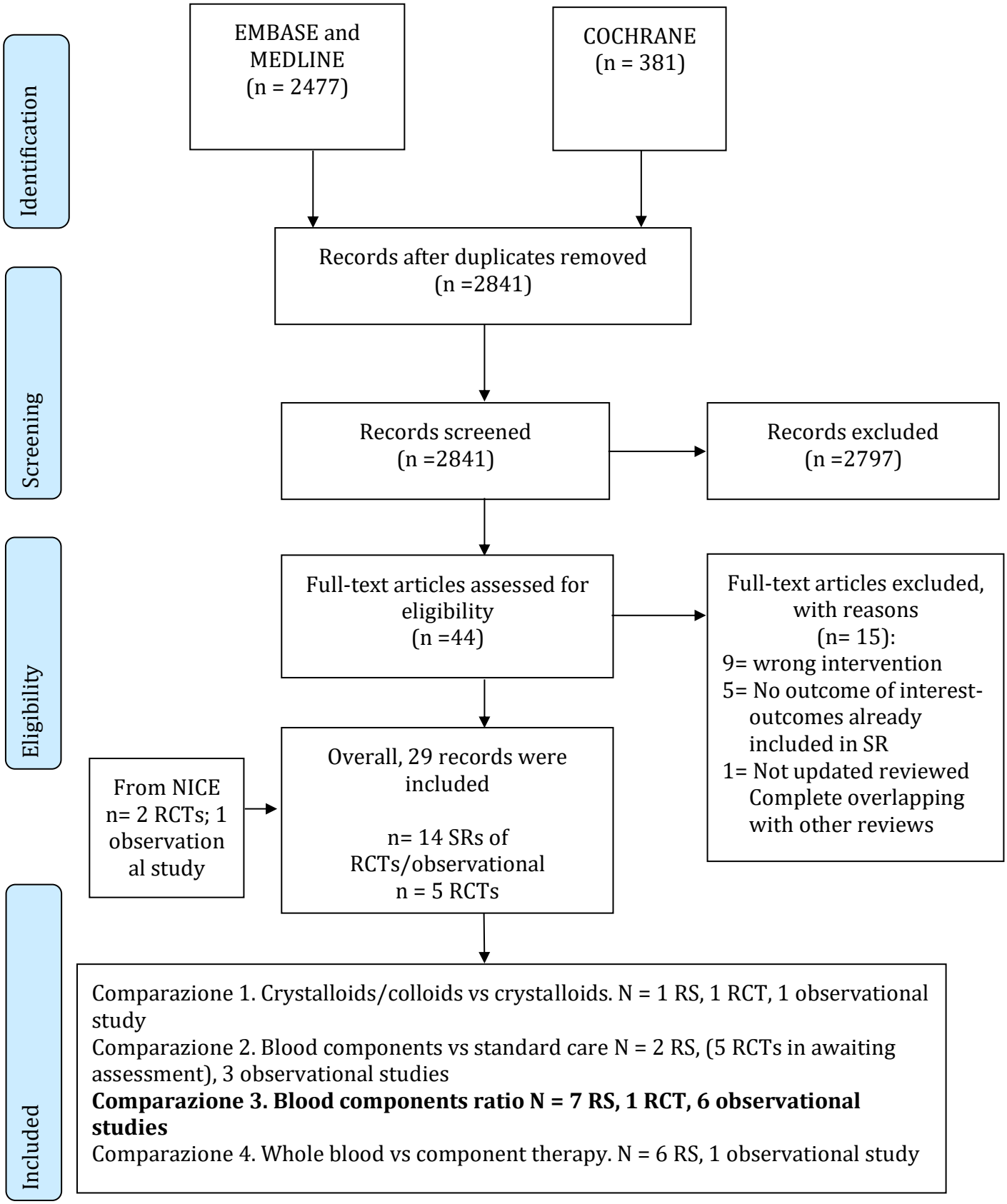
Our model predictedmortality better than Injury Severity Score or Revised Trauma Score parameters and identified 36 unexpected survivors. Compared with expected survivors, unexpected survivors were younger (33 years [24, 52 years] vs. 47 years [32, 59 years], p = 0.013), were more severely injured (Injury Severity Score 34 [22, 50] vs. 18 [10, 27], p < 0.001), had worse organ dysfunction and hospital resource outcomes (multiple organ failure, intensive care unit, hospital length of stay, and ventilator days), and were more likely to receive prehospital plasma (67 vs. 46%, p = 0.031).

Appendice C3 – Comparazione 3: All blood ratio

INDICE

SELEZIONE DEGLI STUDI

Figure 1. Flow Chart of study selection



OUTCOME

E' stata effettutata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono state individuate 7 SR (McQuilten 2018, Luz 2019, Ritchie 2020, Rodriguez 2020, Poole 2016, Rahouma 2016, Wirtz 2020) e 6 studi osservazionali (Butler 2019, Cannon 2017, Cunningham 2019, Haltmeier 2018, Nederpelt 2019, Sehdev 2020) che permettono di rispondere alla alla macro comparazione "All blood ratio" includendo gli outcome critici e importanti.

Per la comparazione "C1- Fresh Frozen Plasma: Platelets: Red Blood Cell Ratios":
sono state incluse 2 SR (McQuilten 2018, Luz 2019, Ritchie 2020) che hanno tutte incluso Holcomb 2015 e Nascimento 2013 (due RCT).

Per la comparazione "C2- Fresh Frozen Plasma: Red Blood Cell Ratios":
sono state incluse 5 SR (Luz 2019, Rodriguez 2020, Poole 2016, Rahouma 2016, Wirtz 2020), di cui due per la sintesi qualitativa (Poole 2016 e Rodriguez 2020). Inoltre dalla ricerca sistematica sono emersi ulteriori 6 studi osservazionali, di cui uno incentrato sul sottogruppo di pazienti con trauma cranico (Haltmeier 2018) e cinque che includevano la sola popolazione pediatrica (Sehdev 2020, Cannon 2017, Butler 2019, Cunningham 2019, Nederpelt 2019).

Per la comparazione "C3- Platelets: Red Blood Cell Ratios":
sono state incluse 2 SR per la sintesi quantitativa (Luz 2019, Wirtz 2020) e due studi osservazionali che includevano la sola popolazione pediatrica (Butler 2019, Cunningham 2019).

C1- Fresh Frozen Plasma: Platelets: Red Blood Cell Ratios

Comparazione: FFP:PLT:PRBC in rapporti 1:1:1 vs 1:1:2

Gli outcome riportati tra le revisioni sistematiche individuate sono riportati in tabella:

Author - year	Study design	Trials assessing the comparisons whole blood vs component therapy	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of	Patient-reported outcomes: return to normal activities psychological
McQuilten 2018	SR (quantitative synthesis)	2 RCT (Nascimento 2013, Holocomb 2015)							
Luz 2019	SR (quantitative synthesis)	2 RCT (Nascimento 2013, Holocomb 2015)							
Ritchie 2020	SR (qualitative synthesis)	2 RCT (Nascimento 2013, Holocomb 2015)							

CRITICAL OUTCOMES

8. Mortality at 24 hours, 30days/1 month, and 12 months

Tre revisioni sistematiche includono l'outcome di interesse. Si riporta di seguito la sintesi descrittiva dei risultati.

Author - year	**Study design**	**Trials assessing the comparisons FFP:PLT:PRBC ratio**	**Mortality at 24 hours, 30 days/1month and 12 months**
McQuilten 2018	SR Quantitative sysntesis	2 RCT(Nascimento 2013, Holocomb 2015)	**Mortality 24 h** RR 0.75(0.52-1.08) Anticipated absolute effects control 170 per 1000, intervention 42 fewer per 1000 (81 fewer to 14 more). Certainty of evidence LOW **Mortality 28 days** The fixed effects pooled RR 1.26 (0.49-3.22), for 28-days mortality, there was a moderate/high level of heterogeneity (I2 = 75%, P = 0.64) (Figure 2).
Luz 2019	SR Quantitative sysntesis	2 RCT(Nascimento 2013, Holocomb 2015)	**Mortality 24 h** There was a lower rate of death from exsanguination at 24 hours (9.2% in 1:1:1 vs. 14.6% in 1:1:2 group; difference: -5.4% (95% CI,-10.4% to -0.5%]; p = 0.03) **Mortality 30 days** The fixed effects pooled OR 1.35 (0.40-4.59), for 30-days mortality, there was a moderate/high level of heterogeneity (I2 = 76%, P = 0.63) (Figure 2).
Ritchie 2020	SR Qualitative sysntesis	2 RCT(Nascimento 2013, Holocomb 2015)	Only for one RCT (Holocomb et al. 2015) was reported: **Mortality 24 h** RR 1.33 (0.93 – 1.92) **Mortality 1 month** RR 1.17 (0.90 – 1.53)

McQuilten 2020

La revisione sistematica McQuilten 2018 riporta l'outcome mortalità sia a 24 ore che a 30 giorni.

- Per la mortalità a 24 ore, i dati provengono da un unico studio randomizzato e controllato, Holocomb et al. 2015, di cui di seguito si riporta la tabella delle evidenze con relativa valutazione della qualità.

Table 3
GRADE quality assessment and summary of findings table

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) Control	Study event rates (%) Intervention	Relative effect (95% CI)	Anticipated absolute effects Control	Anticipated absolute effects Intervention
1:1:1 vs 1:1:2 or laboratory guided: Mortality – 24 h											
680 (1 RCT)	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯ LOW	58/342 (17.0%)	43/338 (12.7%)	RR 0.75 (0.52-1.08)	170 per 1000	42 fewer per 1000 (81 fewer to 14 more)

- Per la mortalità a 28 giorni, i dati provengono da due RCT (Nascimento et al. 2013, Holocomb et al. 2015), di cui si riporta la stima meta-analitica

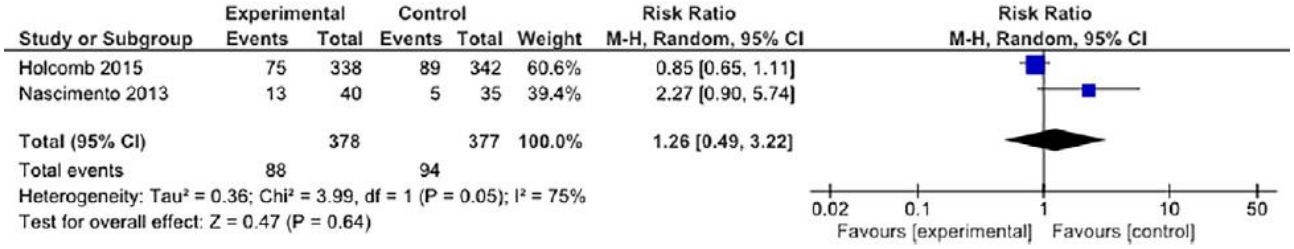


Fig. 2. Forrest plot for 28-day mortality.

Luz 2019

La revisione sistematica Luz 2019 riporta l'outcome mortalità sia a 24 ore che a 30 giorni.

- Per la mortalità a 24 ore, i dati provengono da un unico RCT, Holcomb et al. 2015.
- Per la mortalità a 30 giorni, i dati provengono da due RCT (Nascimento et al. 2013, Holcomb et al. 2015), di cui si riporta la stima meta-analitica

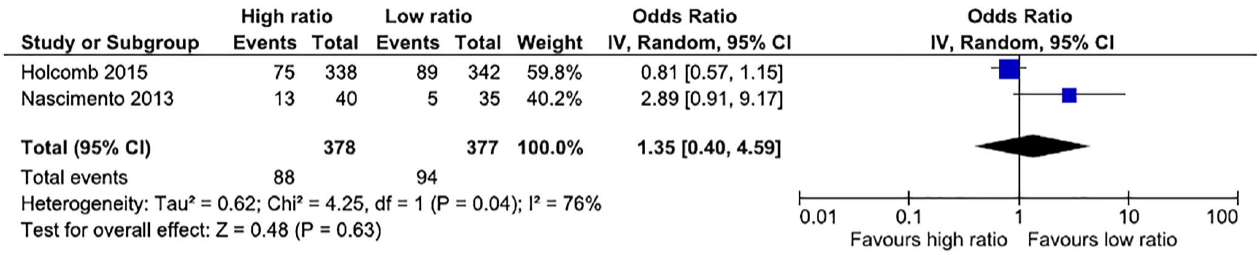


Fig. 2. Thirty-day mortality in RCTs. High ratios in both studies were 1:1:1 (FFP:PLTs:RBCs in Holcomb's and RBCs:FFP:PLTs in Nascimento's trial). Low ratio in Holcomb's trial was 1:1:2 (FFP:PLTs:RBCs) and in Nascimento's trial it was 1.8:1:0.7 (RBCs:FFP:PLTs).

Ritchie 2020

La revisione sistematica riporta solo una sintesi qualitativa e non dati cumulati.

TABLE 4. Mortality/Primary Outcome Data

Author (Date)	24 Hour Mortality (%)		1 Month Mortality (%)	
	n (%)	Relative Risk	n (%)	Relative Risk
Holcomb et al. 2015	Overall: 101/680 (14.85%) I: 58/342 (16.96%) S: 43/338 (12.75%)	1.33 (0.93–1.92)	Overall: 161/680 (23.68%) I: 89/342 (26.02%) S: 75/338 (22.19%)	1.17 (0.90–1.53)
Nascimento et al. 2013	No data	N/A	I: 11/37 (29.7%)	N/A

9. Health related quality of life

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse. Si riporta di seguito la sintesi descrittiva dei risultati.

10. Length of intensive care stay

Due revisioni sistematiche (McQuilten et al. 2018, Ritchie et al. 2020) riportano l'outcome di interesse, senza però riportare una stima meta-analitica. Si riporta di seguito la sintesi descrittiva dei risultati, da cui non emergono differenze statisticamente significative tra i due gruppi.

Author - year	Study design	Trials assessing the comparisons FFP:PLT:PRBC ratio	Length of intensive care stay
McQuilten 2018	SR Quantitative synthesis	2 RCT (Nascimento 2013, Holocomb 2015)	**ICU admission** Nascimento 2013: RR 0.75 (0.60-0.94) **ICU free-days (median [IQR])** Nascimento 2013: I: 23 [12-26]; C: 20 [5-24]; p=0.27 Holocomb 2015: I: 5 [0-11]; C: 4 [0-10]; p=0.10 **Hospital free-days (median [IQR])** Nascimento 2013: I: 0 [0-15]; C: 1.5 [0-12]; p=0.39 Holocomb 2015: I: 1 [0-17]; C: 0 [0-16]; p=0.83
Ritchie 2020	SR Qualitative	2 RCT (Nascimento 2013, Holocomb 2015)	Only for one RCT (Holocomb et al. 2015) was reported: **Length of stay in Days (median [IQR])** I: 0 [0-16]; C: 1 [0-17]

	synthesis		Only for one RCT (Nascimento et al. 2013) was reported: **Hospital free days (median [IQR])** I: 0 [0-15];

11. Adverse effects

Due revisioni sistematiche (McQuilten et al. 2018, Ritchie et al. 2020) riportano l'outcome di interesse, senza però riportare una stima meta-analitica. Si riporta di seguito la sintesi descrittiva dei risultati, da cui non emergono differenze statisticamente significative tra i due gruppi.

Author - year	Study design	Trials assessing the comparisons FFP:PLT:PRBC ratio	Adverse effects
McQuilten 2018	SR Quantitative synthesis	2 RCT (Nascimento 2013, Holocomb 2015)	One RCT (Holocomb et al. 2015) reported the following adverse effect. **Acute respitarory distress syndrome** RR 0.97 (0.67 – 1.41) **Acute kidney injury** RR 0.88 (0.67 – 1.16) **Sepsis** RR 1.10 (0.86 – 1.40) **Multi-organ failure** RR 1.35 (0.70 – 2.59) **Myocardial infarction** RR 0.20 (0.01 – 4.20) **Stroke** RR 0.74 (0.30 – 1.81) **Deep vein thrombosis** RR 1.05 (0.61 – 1.81) **Pulmonary embolus (symptomatic)** RR 1.09 (0.52 – 2.28)
Ritchie 2020	SR Qualitative synthesis	2 RCT (Nascimento 2013, Holocomb 2015)	Only for one RCT (Holocomb et al. 2015) was reported: **Thromboembolic events** RR 0.97 (0.71 – 1.34) **Multiorgan failure** RR 0.74 (0.39 – 1.42) **Sepsis** RR 0.91 (0.71 – 1.16)

12. Acute transfusion reaction

Una revisione sistematica (McQuilten et al. 2018) riporta l'outcome di interesse. Si riporta di seguito la sintesi descrittiva dei risultati, da cui non emergono differenze statisticamente significative tra i due gruppi.

Author - year	Study design	Trials assessing the comparisons FFP:PLT:PRBC ratio	Acute transfusion reaction
McQuilten 2018	SR Quantitative synthesis	2 RCT (Nascimento 2013, Holocomb 2015)	One RCT (Holocomb et al. 2015) reported the following acute transfusion reaction. **Transfusion-related allergenic reaction** RR 2.02 (0.18 – 22.21) **Febrile non-hemolytic transfusion reaction** RR 1.01 (0.06 – 16.11)

			Transfusion-associated circulatory overload RR 3.04 (0.12 – 74.25) **Transfusion-related fatality** RR 3.04 (0.12 – 74.25)

IMPORTANT OUTCOMES

1. Time to definitive control of haemorrhage

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

2. Patient-reported outcomes: pain/discomfort return to normal activities psychological wellbeing)

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

C2- Fresh Frozen Plasma: Red Blood Cell Ratios

Gli outcome riportati tra le revisioni sistematiche individuate sono riportati in tabella:

Author - year	Study design	Trials assessing the comparisons FFB: PRBC ratios	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological
Luz 2019	SR (quantitative and qualitative synthesis)	49 observational studies							
Rodríguez 2020	SR (quantitative and qualitative synthesis)	31 observational studies							
Poole 2016	SR (qualitative synthesis)	8 observational studies							
Rahouma 2016	SR (quantitative synthesis)	32 observational studies							
Wirtz 2020	SR (quantitative synthesis)	2 observational studies							

CRITICAL OUTCOMES

1. Mortality at 24 hours, 30days/1 month, and 12 months

Quattro revisioni sistematiche includono l'outcome di interesse. Si riporta di seguito la sintesi descrittiva dei risultati.

Author - year	Study design	Trials assessing the comparisons FFP vs PRBC	Mortality at 24 hours, 30 days/1month and 12 months
Luz 2019* *some studies of the meta-analysis with wrong intervention and/or comparator	SR	FFP:RBC 1:1 vs <1:1 5 observational studies 2414 participants FFP:RBC 1:1.5 vs <1:1.5 2 observational studies 118 participants FFP:RBC 1:2 vs <1:2 6 observational studies 1388 participants FFP:RBC 1:1 vs <1:1 10 observational studies 4203 participants FFP:RBC 1:1.5 vs <1:1.5 5 observational studies 1369 participants FFP:RBC 1:2 vs <1:2 10 observational studies 2849 participants	**Mortality 24 h** The random effects pooled OR 0.34 (95% confidence [CI] = 0.14–0.82). For 24-hour mortality, there was a high level of heterogeneity (I2 = 88%, P < 0.01). The random effects pooled OR 0.43 (95% confidence [CI] = 0.18–1.06). For 24-hour mortality, there was an absent level of heterogeneity (I2 = 0%, P =0.41). The random effects pooled OR 0.59 (95% confidence [CI] = 0.43–0.81). For 24-hour mortality, there was a low level of heterogeneity (I2 = 22%, P =0.27). **Mortality 30 days** The random effects pooled OR 0.38 (95% confidence [CI] = 0.22–0.68). For 30 days mortality, there was a high level of heterogeneity (I2 = 91%, P <0.01). The random effects pooled OR 0.42 (95% confidence [CI] = 0.22–0.81). For 30 days mortality, there was a moderate/high level of heterogeneity (I2 = 73%, P =0.005). The random effects pooled OR 0.47 (95% confidence [CI] = 0.31–0.71). For 30 days mortality, there was a high level of heterogeneity (I2 = 81%, P <0.01).
Rodríguez 2020	SR	31 observational studies	Qualitative synthesis
Poole 2016	SR	8 observational studies	Qualitative synthesis
Rahouma 2016* *some studies of the meta-analysis with wrong intervention and/or comparator	SR	FFP:RBC <1:1 vs ≥1:1 6 observational studies and 1 RCT 5265 participants FFP:RBC <1:1.5 vs ≥1:1.5 4 observational studies 1877 participants FFP:RBC <1:2 vs ≥1:2 9 observational studies 3540 participants FFP:RBC <1:1 vs ≥1:1 5 observational studies and 2 RCTs 5266 participants	**Mortality 24 h** The random effects pooled OR 2.05 (95% confidence [CI] = 1.55–2.71). For 24-hour mortality, there was a moderate level of heterogeneity (I2 = 57%, P = 0.03). The random effects pooled OR 3.97 (95% confidence [CI] = 1.37–11.49). For 24-hour mortality, there was a high level of heterogeneity (I2 = 88%, P <0.01). The random effects pooled OR 2.85 (95% confidence [CI] = 2.14–3.81). For 24-hour mortality, there was a moderate level of heterogeneity (I2 = 59%, P =0.01). **Mortality 30 days** The random effects pooled OR 1.36 (95% confidence [CI] = 1.09–1.69). For 30 days mortality, there was a

		FFP:RBC <1:1.5 vs ≥1:1.5 5 observational studies 1813 participants FFP:RBC <1:2 vs ≥1:2 14 observational studies 6193 participants	low/moderate level of heterogeneity (I2 = 45%, P =0.09). The random effects pooled OR 2.45 (95% confidence [CI] = 1.14–5.25). For 30 days mortality, there was a high level of heterogeneity (I2 = 87%, P <0.01). The random effects pooled OR 1.77 (95% confidence [CI] = 1.50–2.10). For 30 days mortality, there was a low level of heterogeneity (I2 = 37%, P =0.08).

Luz 2019

For observational cohort studies, mortality was lower in the intervention groups in all three different transfusion ratios of FFP:RBCs assessed (1:1 vs. <1:1, 1:1.5 vs. < 1:1.5, and 1:2 vs. <1:2; Fig. 3). For both 24-hour and 30-day mortality, results were similar, with a survival benefit in the intervention group for the three ratios assessed, demonstrating a dose effect, with increasing ORs from 1:1, 1:1.5, and 1:2 FFP:RBC transfusion ratios.

Mortality at 24 hours: Observational studies

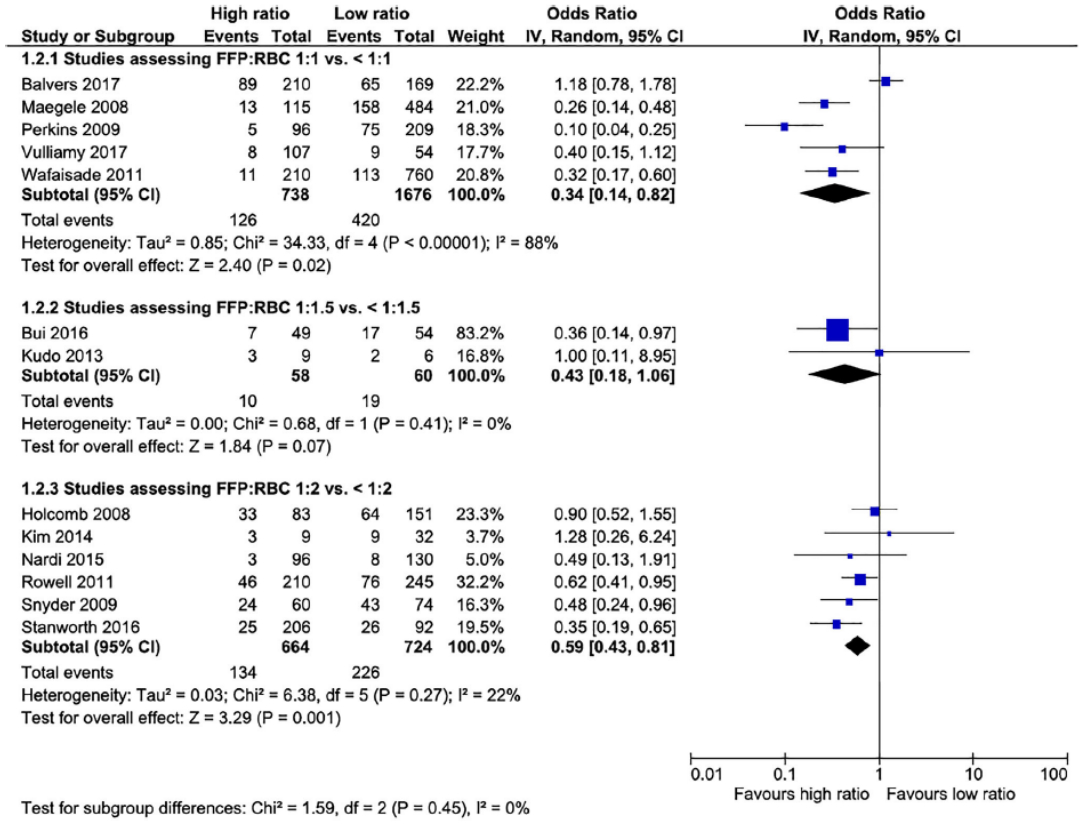


Fig. 3. Twenty-four-hour mortality in non-RCTs according to the FFP:RBC ratio assessed. [Color figure can be viewed at wileyonlinelibrary.com]

**wrong intervention and/or comparator: Holcomb 2011, Perkins 2009, Vulliamy 2017*

Mortality at 30 days: observational studies

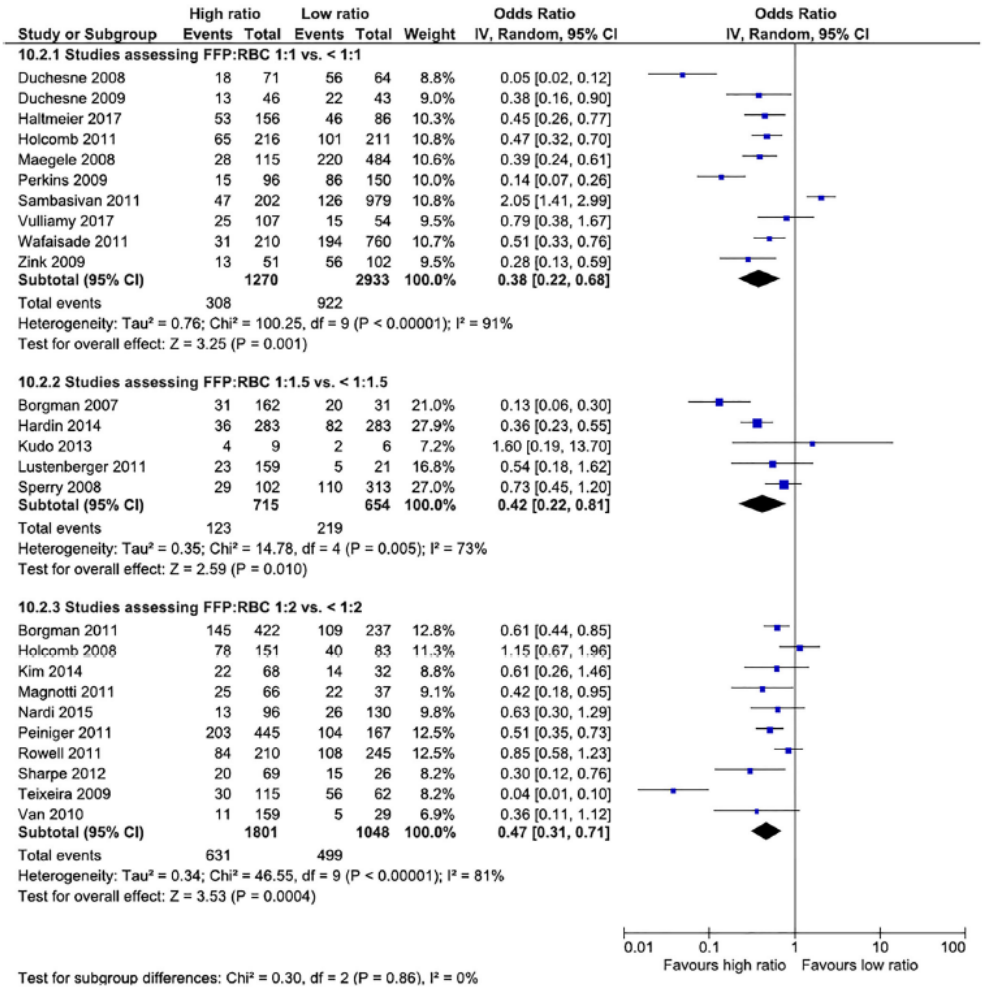


Fig. 4. Thirty-day mortality in non-RCTs according to the FFP:RBC ratio assessed. [Color figure can be viewed at wileyonlinelibrary.com]

**wrong intervention and/or comparator: Holcomb 2011, Perkins 2009, Vulliamy 2017*

Rodriguez 2020*

When analyzing the 31 observational studies (n=13924), the use of a high FFP:RBC ratio was associated with lower early mortality (OR 0.67; 95% CI, 0.60–0.75) and late (OR 0.79; 95% CI, 0.71–0.87), but with a significant heterogeneity for both estimates, with an I2of 91.9% and 86.3%, respectively. There were no differences between the groups when assessing the clinical (n=749) (OR 0,89; 95% CI, 0.64–1.26) and the heterogeneity was high (I2 79.8%). The observational studies took into account the potential differences due to the exclusion of deceased patients over the first 24hours following admission, and hence the summary measurements were stratified (6, 12, and 24hours and studies that did not exclude the deceased patients). The result was that by not excluding the death over the first 24hours, the protective effect on early mortality was maintained (OR 0.58; 95% CI, 0.38–0.89), but that was not the case for late mortality (OR 0.72; 95% CI, 0.46–1.11).

**no distinction among FFP:PRBC ratios.*

Poole 2016

Only qualitative synthesis no cumulative data.

Table 2. Query # 2: Does a fixed blood-plasma transfusion ratio reduce mortality in trauma? Reporting of observational studies included in the revision. The number of patients is referred to those included in the multivariable model. N = number, pts = patients, ctr = centre, FFP = fresh frozen plasma, PRBC = packed red blood cells, OR = odds ratio, HR = hazard ratio, CI = confidence interval, Cont. Var. indicates that variables are used as continuous in the models, when not specified they have been categorized.

First author—Year	N of pts	N of centres	pts/ctr/year	Inclusion criteria	Outcome	Mortality (%)	Mortality OR (95%-CI)*
Scalea– 2008 [31]	NA	1	NA	Patients admitted to the ICU for trauma occurred within 24 hours	Hospital mortality	NA	PRBC:FFP ratio 1:1 0.57 (0.19–1.66). PRBC:FFP ratio (Cont. Var.) 1.23 (0.81–1.87)
Inaba– 2010 [36]	568	1	95	Trauma admitted to surgical ICU receiving < 10 PRBC units within 12 hours from admission (excluding deaths occurred within 24 hours)	Hospital mortality	89 (15.7)	FFP 1.27 (0.81–2.0)
Wafaisade– 2011 [32]	1362	116	3	Patients survived one hour from admission receiving more than 3 and less than 10 PRBC units from arrival to the ER and admission to the ICU	Hospital mortality	321 (23.6)	FFP:PRBC ratio <1:1 reference. FFP:PRBC ratio = 1:1 0.8 (0.54–1.18) FFP:PRBC ratio >1:1 0.52 (0.31–0.87)
Holcomb– 2013 [30]	876	10	79	Trauma patients receiving at least 3 PRBC units within 24 hours from admission	Hospital mortality	NA	FFP:PRBC ratio > = 1:1 HR 0.23 (95%-CI NA) FFP:PRBC ratio: ≥ 1:2 —<1:1 HR 0.42 (95%-CI NA) FFP:PRBC ratio < 1:2 HR ref = 1 (95%-CI NA) FFP:PRBC (Cont. Var.) HR 0.31 (0.16–0.58)
Teixeira– 2009 [35]	383	1	64	Trauma patients receiving 10 or more PRBC units within the first 24 hours	Hospital mortality	161 (42)	FFP:PRBC ratio 0.02 (0.01–0.07)
Sambavisan– 2011 [28]	1181	23	22	Patients receiving at least one but less than 10 PRBC units within 24 hours from admission (excluding patients dies within 2 hours from admission)	Hospital mortality	173 (14.6)	FFP:PRBC ratio ≥1 HR 0.87 (0.55–1.38)
Holcomb– 2011 [34]	643	22	29	Trauma patients receiving 10 or more PRBC units within 24 hours from admission	30-day mortality	181 (28.1)	FFP:PRBC ratio (Cont. Var.) HR 0.49 (0.28–0.86)
Borgman– 2011 [33]	557	100	1	TASH score ≥ 15 excluding patients died within 1 hour from admission	Hospital mortality	NA	FFP:PRBC ratio (Cont. Var.) Survival OR 2.5 (1.56–4.00)§
Mitra– 2010 [27]	331	1	90	Patients receiving more than 4 packed red blood cell units within 4 hours from admission	30-day mortality	99 (29.9)	FFP:PRBC ratio (Cont. Var.) 0.15 (0.05–0.48)

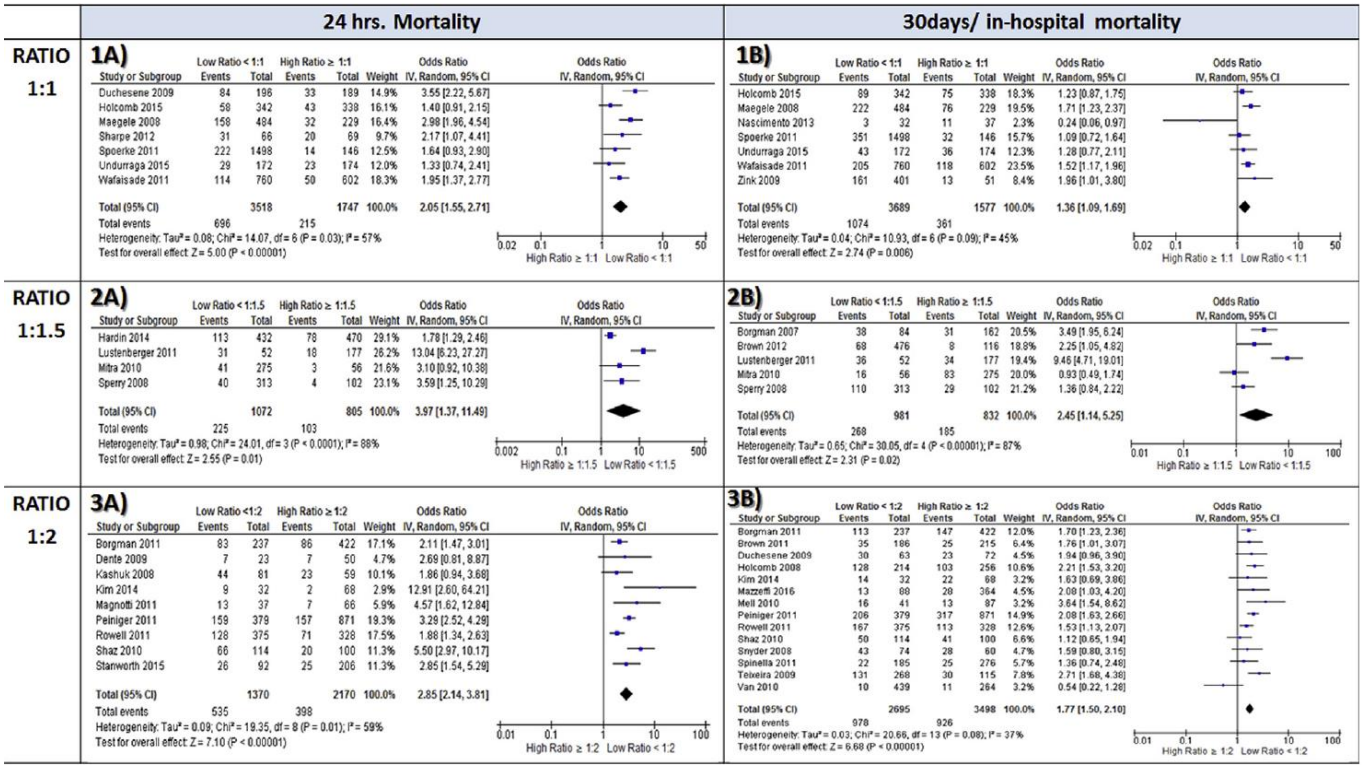
* When the chosen multivariable analysis is a proportional-hazards regression model, the result is preceded by the acronym "HR", in all the other cases ORs from logistic regression are implied.

§ In this case the survival and not the mortality OR was calculated.

Rahouma 2016

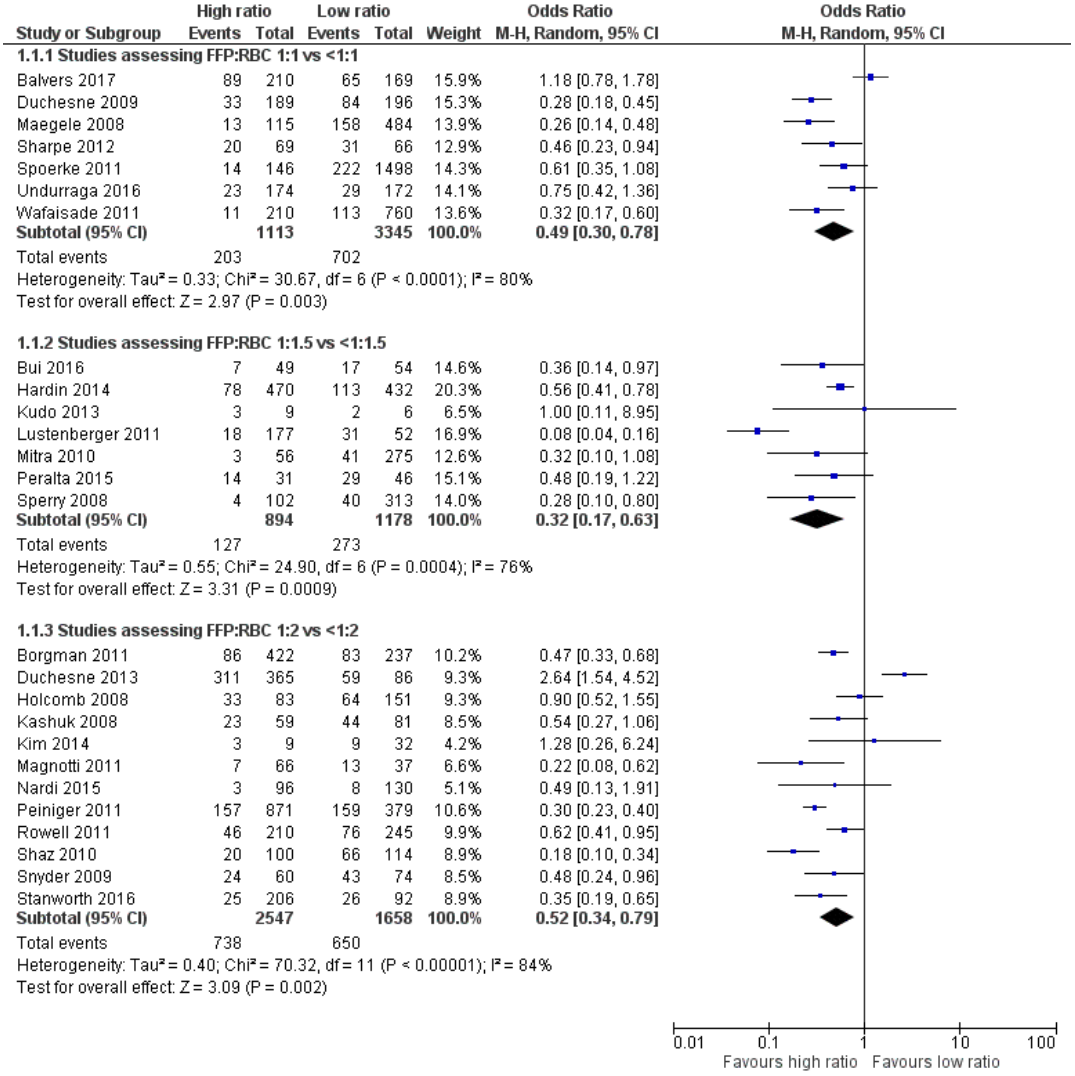
Mortality at 24 hours and 30 days: Observational studies and two RCTs.

The two RCTs (Holcomb 2015; Nascimento 2013) considered a wrong intervention and/or comparator.

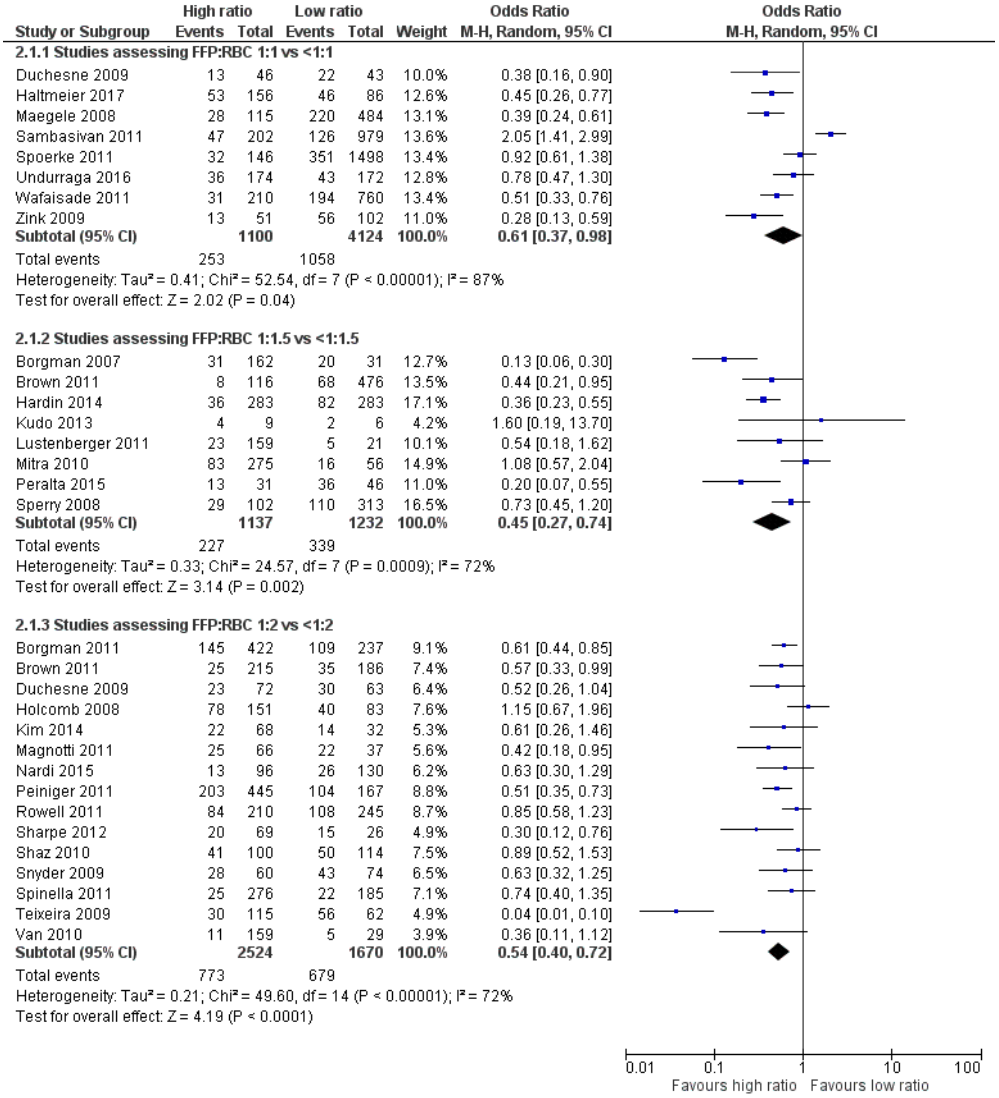


Re-analysis of the included studies in the systematic reviews of Luz 2019, Rodriguez 2020 and Rahouma 2016

Mortality at 24 hours: Observational studies (high ratio vs low ratio)



Mortality at 30 days: Observational studies (high ratio vs low ratio)



8. *Subgroup: patients with TBI*

Mortality at 24 hours

Haltmeier 2018

Patients of all ages with isolated severe blunt traumatic brain injury (TBI) that received PRBC transfusion within the first 24 h after hospital admission were included. Transfusion ratios were then dichotomized using the transfusion of at least one unit plasma per unit PRBC (plasma:PRBC≥1). Patients with plasma:PRBC transfusion ratios ≥1 had a significantly decreased in-hospital mortality when compared to patients with plasma:PRBC transfusion ratios < 1 in both all patients included (34.0% vs. 53.5%, p = 0.005) and the subgroup of patients with early mortality excluded (24.8% vs. 42.0%, p = 0.018).

Table 2
Univariate analysis of mortality.

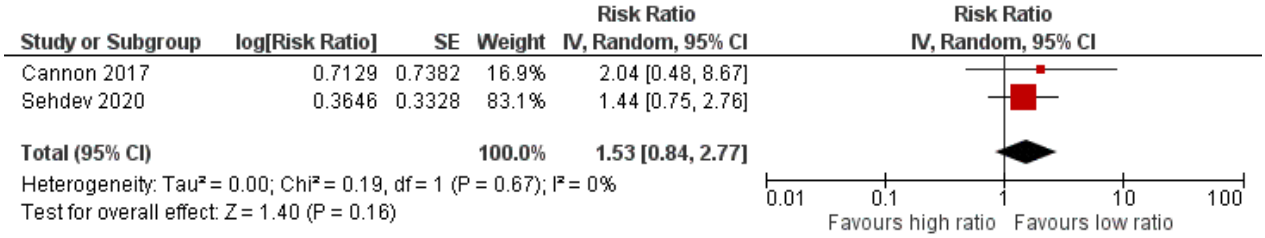
	Survived number (%)	Died number (%)	p-value[‡]
All patients	250 (64.9)	135 (35.1)	
Plasma* to PRBC ratio			
Overall			
Plasma:PRBC < 1	40 (46.5)	46 (53.5)	0.005
Plasma:PRBC ≥ 1	103 (66.0)	53 (34.0)	
Early mortality excluded			
Plasma:PRBC < 1	40 (58.0)	29 (42.0)	0.018
Plasma:PRBC > 1	103 (75.2)	34 (24.8)	

[‡]Pearson's Chi-square with continuity correction. [†]Univariate logistic regression analysis.
*Plasma: Fresh Frozen Plasma (FFP), plasma frozen within 24 h (FP24), thawed plasma.
PRBC: Packed Red Blood Cells, PLT: Platelets.

Meta-analysis of the observational studies

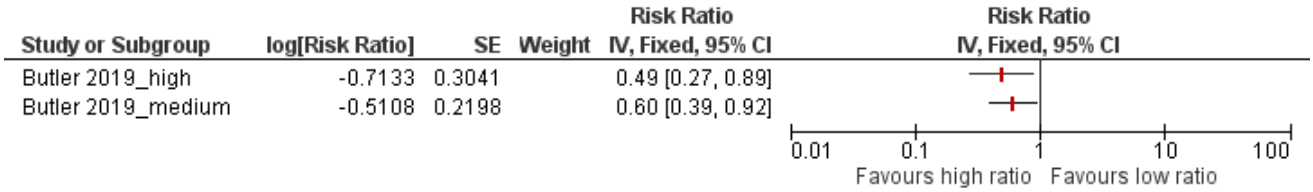
Pediatric population

Mortality at 24 hours: high ratio (≥1:2) vs low ratio (<1:2)



Study	Comparison	Adjustments
Cannon 2017	Low (<1:2) and high (≥1:2) ratios of PLAS/PRBC 1:2	age, sex, international normalized ratio, injury severity score, and PLAS/PRBC ratio
Sehdev 2020	PRBC: plasma ratio of > 2:1 (Unbalanced Ratios, UR) versus ≤ 2:1 (Balanced Ratios, BR)	age, injury severity score, and severe head injury

Mortality at 24 hours: high ratio (≥1:1) or medium (≥1:2 & <1:1), vs low (<1:2)



Study	Comparison	Adjustments
Butler 2019	FFP:PRBC ratio: low (<1:2), medium (≥1:2 & <1:1), and high (≥1:1)	age, injury mechanism, hypotension, abnormal heart rate, Glasgow coma scale, injury severity score, need for mechanical ventilation and transfer status

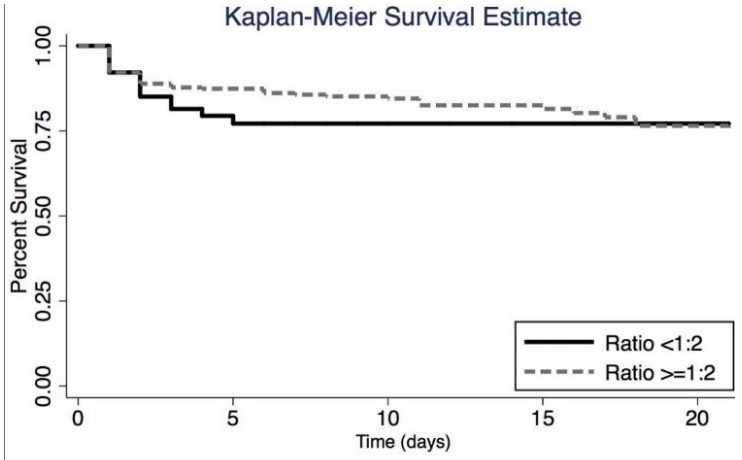
Cannon 2017

Low (LO) and high (HI) ratios of PLAS/PRBC 1:2. The primary endpoints were 24-hour and in-hospital mortalities. Univariate analysis demonstrated no difference in mortality in the LO versus HI ratio groups at 24 hours (9.2% vs. 8.0%, p = 0.75) or at discharge (21.5% vs. 17.1%, p = 0.39) (Table 3). Kaplan-Meier analysis also demonstrated no mortality difference between these groups over time.

TABLE 3. Patient Outcomes

	LO Ratio (<1:2) n = 65	HI Ratio (≥1:2) n = 299	*p*
Died < 24 h	6 (9.2%)	24 (8.0%)	0.75
Died in hospital	14 (21.5%)	52 (17.1%)	0.39
Time to death, d	2 (1–3)	2 (1–6)	0.50

Data are presented as n (%) or median (IQR).



SDC Figure 1. Kaplan-Meier analysis of mortality over time in the LO (solid line) vs. HI (dashed line) ratio groups. Log-rank p=0.37 and Wilcoxon test p=0.29.

Cox regression analysis was used to determine an association between ratio of PLAS/RBC and mortality while controlling for significant differences between survivors and nonsurvivors. The proportionality assumption was not violated (p = 0.48). Included variables were age, sex, INR, ISS, and PLAS/PRBC ratio. A total of 205 (56.3%) patients had complete covariate data. Female sex, INR and ISS were independently associated with mortality, but a HI ratio of PLAS/PRBC was not.

TABLE 4. Cox Proportional Hazard Regression for Hospital Mortality (n = 205)

Covariate	HR	95% CI	*p*
Age	0.98	0.90–1.09	0.84
Female sex	2.41	1.18–4.92	0.02
ED INR	1.73	1.30–2.31	<0.01
ISS	1.05	1.03–1.07	<0.01
HI Ratio PLAS/PRBC (≥1:2)	2.04	0.48–8.73	0.34

HR, hazard ratio; CI, confidence interval.

Analysis including **patients with TBI**.

SDC TABLE 2. Multivariable logistic regression for hospital mortality including head injured patients (n=286)

Covariate	OR	95% CI	*p*
Age	1.00	0.94-1.08	0.88
Female Gender	1.84	1.06-3.17	**0.03**
ED INR	1.58	1.32-1.89	**<0.01**
ISS	1.04	1.03-1.06	**<0.01**
HI Ratio PLAS:PRBC (≥1:2)	1.06	0.47-2.39	0.90

Butler 2019

The patients were divided into three groups based on their FFP:PRBC ratio at 24h: low (<1:2), medium (≥1:2 and <1:1) and high (≥1:1). The primary outcome was 24h mortality. After 24h, the primary causes of death shift from hemorrhage to traumatic brain injury (TBI), organ failure, and infection. Mortality at 24h was 19.7% (95% CI: 16.6 to 23.2%) and in-hospital mortality was 42.4% (95% CI: 38.3 to 46.5%).

		FFP:PRBC		
	All massive transfusion	**Low <1:2**	**Med ≥1:2 & <1:1**	**High ≥1:1**
	n=583	n=232	n=215	n=136
Mortality				
24h mortality, No. (%)	115 (19.7)	55 (23.7)	44 (20.5)	16 (11.8)
In hospital mortality, No. (%)	247 (42.4)	104 (44.8)	97 (45.1)	46 (33.8)
Time to death, median (IQR), h	28 (6 to 56)	19 (5 to 50)	31 (8 to 62)	40 (18 to 66)

In sensitivity analyses, the association of FFP:PRBC ratio with 24h mortality remained significant in the subset of 166 patients **without severe TBI** (aRR 0.09, 95% CI: 0.01 to 0.63).

Multivariable Poisson regression analysis evaluating the association between blood component ratios and 24h mortality in 583 massively transfused pediatric trauma patients.[a]

Independent Variables	aRR	95% CI
24h blood products		
FFP:PRBC ratio, categorical		
Low <1:2	1 (Ref)	
Med ≥1:2 & <1:1	0.60	0.39–0.92
High ≥1:1	0.49	0.27–0.87

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; FFP, fresh frozen plasma; PRBC, packed red blood cells.

[a]Model adjusted for age, injury mechanism, hypotension, abnormal heart rate, Glasgow coma scale, injury severity score, need for mechanical ventilation, and transfer status.

Sehdev 2020

various ratios of transfusions for pediatric trauma patients (PTPs) receiving a massive transfusion (MT) are unknown. We compared PRBC: plasma ratio of > 2:1 (Unbalanced Ratios, UR) versus ≤ 2:1 (Balanced Ratios, BR), hypothesizing decreased risk of mortality (within 24 h) with BR. After adjusting for covariates, there was no difference in associated risk of mortality when comparing patients receiving an UR compared to a BR (OR 1.44, CI 0.75–2.78, p = 0.271).

Table 2 Multivariate analysis of risk of mortality in pediatric trauma patients receiving unbalanced ratios of MT resuscitation versus balanced ratios of MT resusciatation, adjusting for age, ISS, and severe head injury

Risk factors	Odds ratio	CI	*p* value
UR of MT Resuscitation	1.44	0.75–2.78	0.271
Age	0.95	0.89–1.02	0.174
ISS	2.35	1.06–5.18	0.035
Severe Head Injury	5.27	2.71–10.2	<0.001
Pancreas Injury	1.18	0.17–8.09	0.867

CI confidence interval, *ISS* injury severity score, *MT* massive transfusion, *UR* unbalanced ratio (> 2:1 PRBC:Plasma), *BR* balanced Ratio (≤ 2:1 PRBC:Plasma)

On a sub-analysis, patients that received **severely UR** of ≥ 4:1 PRBC: plasma compared to a BR of ≤ 2:1 (OR 1.42 CI 0.53–3.80, p = 0.489) still had no difference in associated risk of mortality. (See Table 3).

Table 3 Multivariable analysis of risk of mortality in pediatric trauma patients receiving unbalanced ratios of MT (≥ 4:1) versus balanced ratios of MT (≤ 2:1), adjusting for age, ISS, and severe head injury

Risk factors	Odds ratio	CI	*p* value
UR of MT Resuscitation	1.42	0.53–3.80	0.489
Age	0.97	0.88–1.06	0.451
ISS	3.22	1.18–8.82	0.023
Severe Head Injury	5.02	2.32–10.87	<0.001

CI confidence Interval, *ISS* injury severity score, *MT* massive transfusion, *UR* unbalanced ratio (≥ 4:1 PRBC:Plasma), *BR* balanced ratio (≤ 2:1 PRBC:Plasma)

The analysis for patients **1–12 years old** (n = 90) showed that there was no difference in the associated risk of mortality between those receiving BR and UR (OR 1.71, CI 0.65–4.50, p = 0.277). For those aged **13-to-17 years old** (n = 149), there was again no difference in the associated risk of mortality between those receiving BR and UR (OR 1.58, CI 0.60–4.16, p = 0.351).
PTPs in the BR group had a mortality rate of 46.1% compared to 52% in the UR group (p = 0.366). PTPs receiving BR after **penetrating trauma** had a similar mortality rate compared to those receiving UR (41.4% vs 46.7%, p = 0.737). PTPs receiving BR after **blunt trauma** had a similar mortality rate compared to those receiving UR (48.3% vs. 55.6%, p = 0.464).

Table 4 Clinical outcomes in pediatric trauma patients receiving unbalanced ratios of MT resuscitation versus balanced ratios of MT resuscitation

Outcomes	MT ($n=239$)	BR ($n=141$)	UR ($n=98$)	p value
Mortality, n (%)				
All mortality	116 (48.5%)	65 (46.1%)	51 (52.0%)	0.366
Mortality among Blunt trauma	54 (51.4%)	29 (48.3%)	25 (55.6%)	0.464
Mortality among Penetrative trauma	19 (43.2%)	12 (41.4%)	7 (46.7%)	0.737

Nederpelt 2019

Different FFP:pRBC ratios (patients were assigned to 7 ratio cohorts (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, and over 1:6 [1:6+]). 24-hour mortality and in-hospital mortality. Table 4 summarizes the multivariable regression analyses findings. In summary, adjusting for all confounders related to patient demographics, patient comorbidities, injury characteristics, and hospital/management details, the 1:1 ratio cohort had the lowest odds of 24-hour mortality. As important, compared to the 1:1 ratio, the odds of mortality independently and incrementally increased to 1.23 (95% CI 1.02 to 1.48) for a 1:2 ratio, 2.11 (95% CI 1.42 to 3.13) for 1:4, and as high as 4.11 (95% CI 2.31 to 7.31) for 1:5 (Fig. 1 and Table 4, all p < 0.05).

Table 4. 24-Hour Mortality for Each of the 7 Different Fresh Frozen Plasma-to-Packed Red Blood Cell Ratio Cohorts

Variable	1: 1	1: 2	1: 3	1: 4	1: 5	1: 6	1: 6+	p Value
24-h mortality								
Odds ratio (95% CI)	Reference	1.23 (1.02–1.48)	1.62 (1.24–2.11)	2.11 (1.42–3.13)	4.11 (2.31–7.31)	2.98 (2.31–6.13)	1.25 (0.94–1.67)	
Incidence, n (%)	395 (28.38)	598 (33.20)	200 (40.65)	91 (47.89)	49 (62.03)	29 (56.86)	135 (31.99)	<0.0001
In-hospital mortality								
Odds ratio (95% CI)	Reference	1.16 (0.90–1.49)	1.51 (1.03–2.20)	1.52 (0.92–2.49)	3.64 (1.84–7.22)	2.65 (1.14–6.13)	1.43 (1.14–6.13)	
Incidence, n (%)	675 (48.49)	888 (49.31)	266 (54.07)	108 (56.84)	56 (70.89)	36 (70.59)	203 (48.10)	<0.0001

2. *Health related quality of life :*

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

3. *Length of intensive care stay*

Pediatric population

Sehdev 2020

Various ratios of transfusions for pediatric trauma patients (PTPs) receiving a massive transfusion (MT) are unknown. We compared PRBC: plasma ratio of > 2:1 (Unbalanced Ratios, UR) versus ≤ 2:1 (Balanced Ratios, BR).

Table 4 Clinical outcomes in pediatric trauma patients receiving unbalanced ratios of MT resuscitation versus balanced ratios of MT resuscitation

Outcomes	MT ($n=239$)	BR ($n=141$)	UR ($n=98$)	p value
LOS, days, median (IQR)		9 (27)	8.5 (21)	0.900
ICU, days, median (IQR)		5 (13)	4 (11)	0.722
Ventilator, days, median (IQR)		3 (5)	3 (8)	0.304

Cannon 2017

Low (LO) and high (HI) ratios of PLAS/PRBC 1:2,. Length of stay (LOS), intensive care unit (ICU)–free days.

TABLE 3. Patient Outcomes

	LO Ratio (<1:2) n = 65	HI Ratio (≥1:2) n = 299	*p*
Mechanical ventilation	54 (83.1%)	257 (86.0%)	0.55
Ventilator-free days	26 (22–27)	24 (18–26)	0.05
ICU-free days	24 (16–26)	22 (14–26)	0.16
Hospital LOS	5 (2–12)	8 (3–15)	0.01

Data are presented as n (%) or median (IQR).

Butler 2019

The patients were divided into three groups based on their FFP:PRBC ratio at 24h: low (<1:2), medium (≥1:2 and <1:1) and high (≥1:1). Secondary outcomes included in-hospital mortality and a predetermined list of complications. Hospital length of stay, intensive care unit (ICU) length of stay, ventilator days, and hospital disposition were evaluated for surviving patients. Among survivors, median hospital length of stay was 20 (IQR: 12 to 30) days and median ICU length of stay was 12 (IQR: 6 to 19) days.

		FFP:PRBC		
	All massive transfusion	**Low <1:2**	**Med ≥1:2 & <1:1**	**High ≥1:1**
Outcomes of survivors	n=336	n=128	n=118	n=90
Hospital length of stay, median (IQR), d	20 (12 to 30)	19 (12 to 29)	20 (11 to 32)	22 (13 to 31)
ICU length of stay, median (IQR), d	12 (6 to 19)	12 (6 to 18)	10 (5 to 20)	13 (7 to 18)
Ventilator days, median (IQR), d	8 (3 to 13)	8 (3 to 13)	7 (3 to 14)	8 (4 to 13)

Multivariable regression analysis evaluating secondary outcomes in 583 massively transfused pediatric trauma patients.[a]

Secondary Outcomes	FFP:PRBC ratio		Platelet:PRBC ratio	
	aRR	95% CI	aRR	95% CI
Outcomes of survivors				
Hospital length of stay	8.56	0.89–81.82		
ICU length of stay	0.84	0.18–4.03	1.92	0.05–69.53
Mechanical ventilation	1.02	0.88–1.18	0.97	0.67–1.42
Ventilator days	0.77	0.16–3.81	0.77	0.02–35.37

[a] Models adjusted for age, injury mechanism, hypotension, abnormal heart rate, Glasgow coma scale, injury severity score, need for mechanical ventilation, and transfer status.

Cunningham 2019

Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1. Ventilator, ICU, and hospital-free days, as well as other in-hospital complications were similar among all groups.

Table 2 – Twenty-four hours Plasma:RBC ratio outcomes.

	Low <1:2 (*n* = 163)	Medium ≥1:2 to <1:1 (*n* = 176)	High ≥1:1 (*n* = 126)	*P*
ICU-free d	7 (0-19)	2 (0-21)	12 (0-20)	0.18
Ventilator-free d	11 (0-21)	8 (0-23)	17 (0-23)	0.05
Hospital-free d	0 (0-13)	0 (0-10)	0 (0-11)	0.67

Nederpelt 2019

Different FFP:pRBC ratios (patients were assigned to 7 ratio cohorts (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, and over 1:6 [1:6+]). ICU length of stay. Moreover, the 1:1 ratio cohort had the longest hospital and ICU lengths of stay (12 ± 13 days, p < 0.0001 and 18 ± 22 days, p < 0.0001, respectively).

Variable	1: 1	1: 2	1: 3	1: 4	1: 5	1: 6	1: 6+	p Value	p < 0.05 on multivariable regression
ICU LOS, mean (SD)	12 (13)	12 (15)	10 (11)	10 (13)	7 (7)	10 (12)	10 (11)	<0.0001	No
LOS, d, mean (SD)	18 (22)	17 (22)	14 (18)	12 (21)	7 (12)	10 (20)	14 (19)	<0.0001	Yes
Unplanned ICU readmission, n (%)	48 (3.45)	47 (2.61)	10 (2.03)	1 (0.53)	0	2 (3.92)	9 (2.13)	0.108	No

4. Adverse effects

Due revisioni sistematiche riportano l'outcome di interesse. Di seguito si riporta una tabella riassuntiva dei risultati.

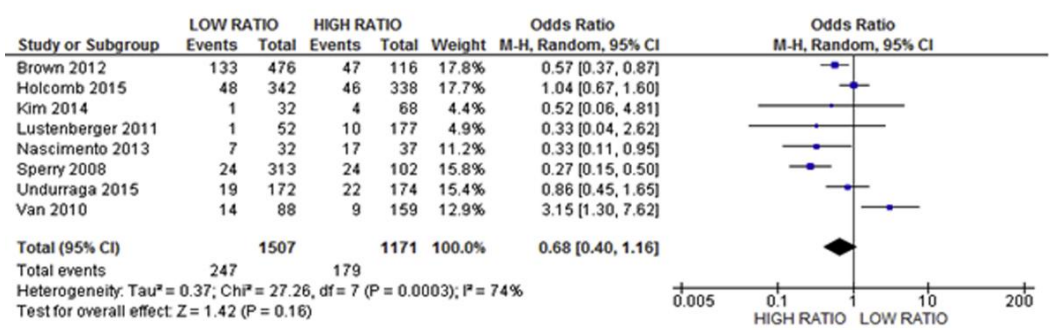
Author – year	Study design	Comparisons FFP vs PRBC	Adverse effects
Rahouma 2016	SR	High:Low ratio (FFP:PRBC)	**Acute respiratory distress syndrome** Six observational studies and two RCTs (Holcomb 2015; Nascimento 2013 that reported the wrong intervention and/or comparator) reported rates of ARDS. There was no difference in the incidence of ARDS with respect to FFP: RBC ratio (OR: 0.68, CI 0.40-1.16, P = 0.16). **Acute lung injury** An observational study and one RCT (Holcomb 2015 that considered a wrong intervention and/or comparator) reported the incidence of ALI. no differences were observed in the incidence of ALI (OR: 1.23, CI 0.81-1.86, P = 0.34)
Wirtz 2020	SR	<1:2 (low ratio), 1-2:2 (high ratio)	**Thromboembolic events** Two observational studies and one RCT (Holcomb 2015 that reported the wrong intervention and/or comparator). Results of three of these studies could be pooled based on their definition of high and low transfusion ratio, which showed no increased risk for TEEs with the use of high plasma-to-RBC ratios hen compared to a low plasma-to-RBC ratio (OR, 1.34; 95% CI, 0.28-1.56; p = 0.34; Fig. 3). Only one study reported on patients being transfused in an inverse ratio and could therefore not be pooled in our analysis.

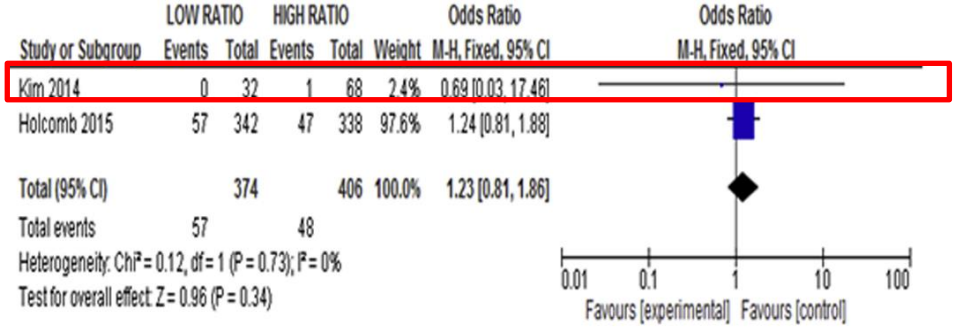
Rahouma 2016

Acute respiratory distress syndrome (ARDS) and Acute lung injury (ALI): Observational studies and two RCTs (Holcomb 2015; Nascimento 2013).

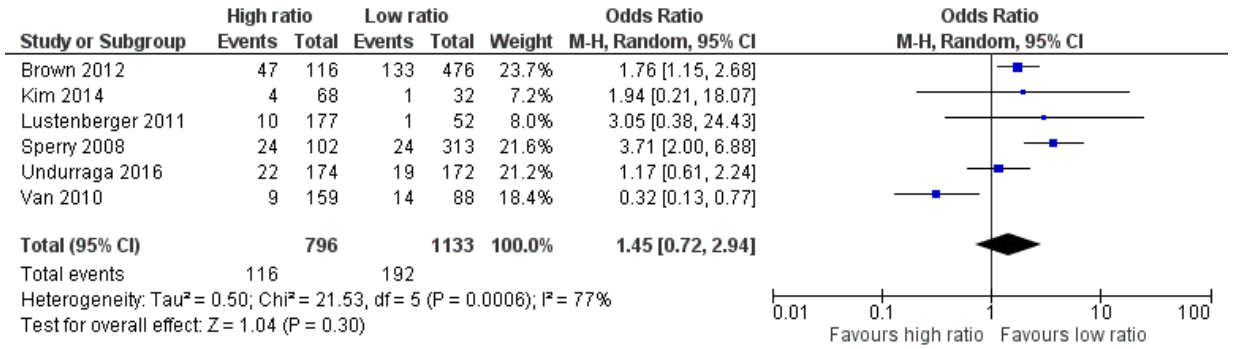
The two RCTs considered a wrong intervention and/or comparator.

There was no difference in the incidence of ARDS with respect to FFP: RBC ratio (OR: 0.68, CI 0.40-1.16, P = 0.16) (figure on the left). Similarly, no differences were observed in the incidence of ALI (OR: 1.23, CI 0.81-1.86, P = 0.34) (figure on the right).





ADRS without the two RCTs (high ratio vs low ratio):



Wirtz 2020

Thromboembolic events: Two observational studies and one RCT (Holcomb 2016).

The RCT considered a wrong intervention and/or comparator.

Results of three of these studies could be pooled based on their definition of high and low transfusion ratio, which showed no increased risk for TEEs (thromboembolic events) with the use of high plasma-to-RBC ratios hen compared to a low plasma-to-RBC ratio (OR, 1.34; 95% CI, 0.28-1.56; p = 0.34; Fig. 3). Only one study reported on patients being transfused in an inverse ratio and could therefore not be pooled in our analysis.

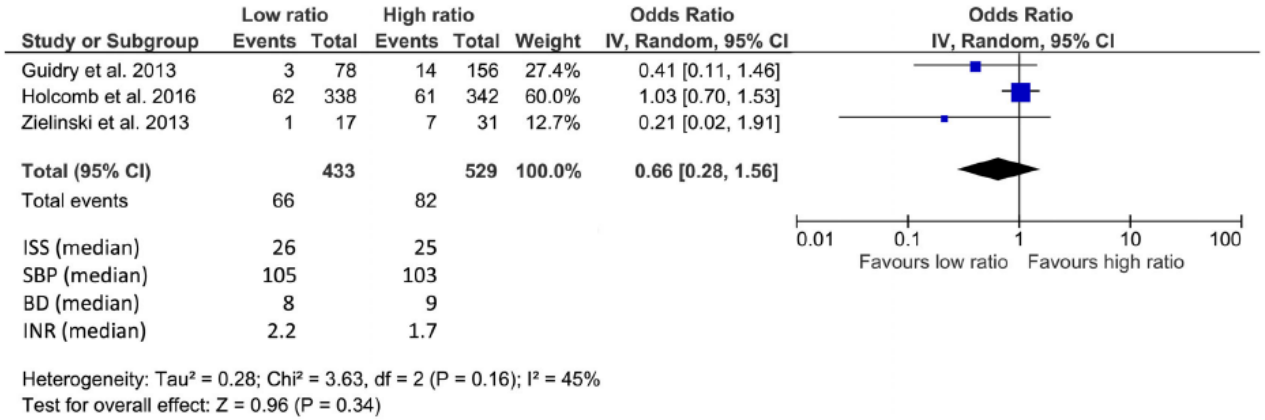
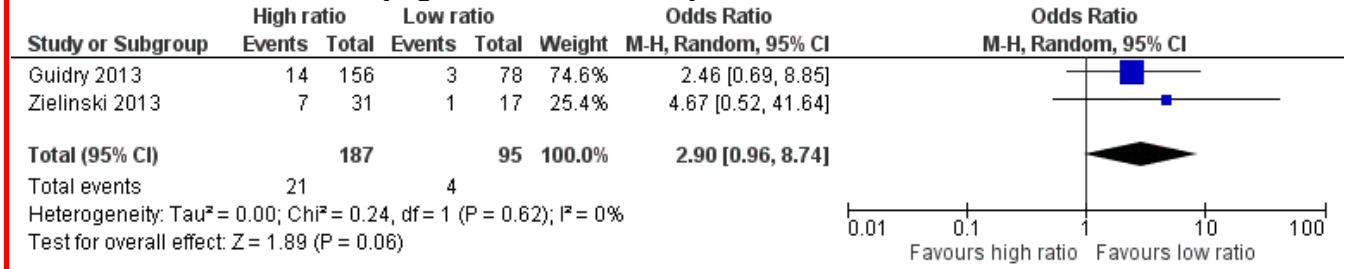


Fig. 3. RBC-to-FFP ratio and the development of thromboembolic events in trauma. BD = base deficit; INR = international normalized ratio; SBP = systolic blood pressure. [Color figure can be viewed at wileyonlinelibrary.com]

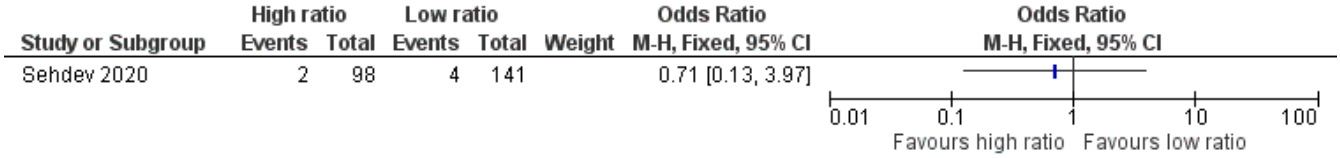
TEE without the two RCTs (high ratio vs low ratio):



Pediatric population

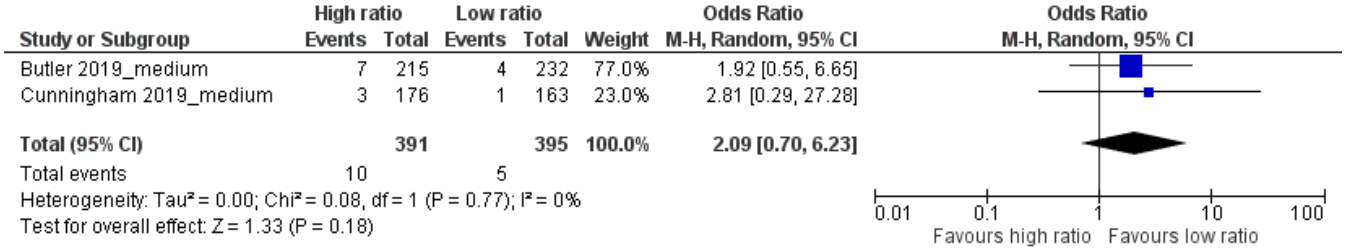
E' stata trovata eterogeneità nella misurazione degli eventi avversi e delle complicanze. Per trasparenza e completezza di informazione si riportano di seguito i singoli studi, e laddove possibile le stime pooled.

ADRS, unadjusted estimates: high ratio (>1:2) vs low ratio (≤ 2:1)



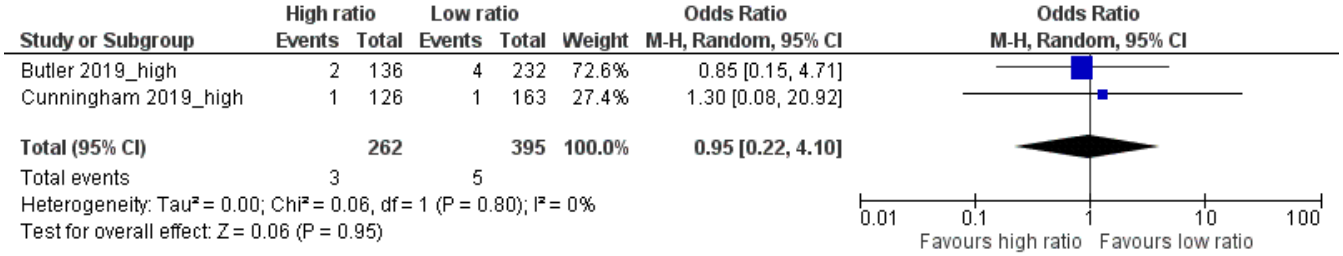
Study	Comparison
Sehdev 2020	PRBC: plasma ratio of > 2:1 (Unbalanced Ratios, UR) versus ≤ 2:1 (Balanced Ratios, BR)

ADRS, unadjusted estimates: medium (≥1:2 to <1:1) vs low ratio (<1:2)



Study	Comparison
Butler 2019	FFP:PRBC ratio: low (<1:2), medium (≥1:2 & <1:1), and high (≥1:1)
Cunningham 2019	Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1

ADRS, unadjusted estimates: (high ≥1:1) vs low ratio (<1:2)



Study	Comparison
Butler 2019	FFP:PRBC ratio: low (<1:2), medium (≥1:2 & <1:1), and high (≥1:1)
Cunningham 2019	Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1

Butler 2019

The patients were divided into three groups based on their FFP:PRBC ratio at 24h: low (<1:2), medium (≥1:2 and <1:1) and high (≥1:1). Secondary outcomes included in-hospital mortality and a predetermined list of complications. The rate of any complication was low at 15.6%. The most common complication was deep vein thrombosis (DVT) (n=25, 4%), followed by pneumonia (n=20, 3%).

		FFP:PRBC		
	All massive transfusion	**Low <1:2**	**Med ≥1:2 & <1:1**	**High ≥1:1**
	n=583	n=232	n=215	n=136
Complications, No. (%)				
Any	93 (15.6)	28 (12.1)	39 (18.1)	26 (19.1)
Deep vein thrombosis	25 (4.3)	6 (2.6)	10 (4.7)	9 (6.6)
Pneumonia	20 (3.4)	5 (2.2)	10 (4.7)	5 (3.7)
Unplanned return to operating room	16 (2.7)	5 (2.2)	6 (2.8)	5 (3.7)
Acute respiratory distress syndrome	13 (2.2)	4 (1.7)	7 (3.3)	2 (1.5)
Acute kidney injury	11 (1.9)	2 (0.9)	6 (2.8)	3 (2.2)
Unplanned intubation	9 (1.5)	5 (2.2)	3 (1.4)	1 (0.7)
Stroke	8 (1.4)	1 (0.4)	4 (1.9)	3 (2.2)
Severe sepsis	5 (0.9)	2 (0.9)	2 (0.9)	1 (0.7)
Extremity compartment syndrome	4 (0.7)	0 (0)	2 (0.9)	2 (1.5)
Pulmonary embolism	3 (0.5)	1 (0.4)	2 (0.9)	0 (0)

Sehdev 2020

Various ratios of transfusions for pediatric trauma patients (PTPs) receiving a massive transfusion (MT) are unknown. We compared PRBC: plasma ratio of > 2:1 (Unbalanced Ratios, UR) versus ≤ 2:1 (Balanced Ratios, BR), hypothesizing decreased risk of mortality with BR. There was no difference in all complications including AKI, pneumonia, DVT, ARDS, and cardiac arrest (all p > 0.05).

Table 4 Clinical outcomes in pediatric trauma patients receiving unbalanced ratios of MT resuscitation versus balanced ratios of MT resuscitation

Outcomes	MT ($n=239$)	BR ($n=141$)	UR ($n=98$)	p value
Complications, n (%)				
Acute Kidney Injury	10 (4.2%)	8 (5.7%)	2 (2.0%)	0.168
ARDS	6 (2.5%)	4 (2.8%)	2 (2.0%)	0.699
Cardiac Arrest	39 (16.3%)	20 (14.2%)	19 (19.4%)	0.284
Decubitus	15 (6.3%)	13 (9.2%)	2 (2.0%)	0.024
Deep Infection	4 (1.7%)	3 (2.1%)	1 (1.0%)	0.512
Deep Venous Thrombosis	15 (6.3%)	8 (5.7%)	7 (7.1%)	0.645
Compartment Syndrome Extremity	1 (0.4%)	0 (0.0%)	1 (1.0%)	0.229
Organ Space Infection	3 (1.3%)	3 (2.1%)	0 (0.0%)	0.146
Pneumonia	6 (2.5%)	3 (2.1%)	3 (3.1%)	0.650
Pulmonary Embolism	2 (0.8%)	0 (0.0%)	2 (2.0%)	0.088
CVA	6 (2.5%)	5 (3.5%)	1 (1.0%)	0.220
Superficial Infection	4 (1.7%)	3 (2.1%)	1 (1.0%)	0.512
Urinary Tract Infection	6 (2.5%)	4 (2.8%)	2 (2.0%)	0.699
CRBSI	2 (0.8%)	2 (1.4%)	0 (0.0%)	0.236
Unplanned OR	8 (0.3%)	4 (2.8%)	4 (4.1%)	0.599
Unplanned ICU	4 (1.7%)	3 (2.1%)	1 (1.0%)	0.512
Severe Sepsis	3 (1.3%)	2 (1.4%)	1 (1.0%)	0.786
CAUTI	1 (0.4%)	1 (0.7%)	0 (0.0%)	0.403
CLASBI	1 (0.4%)	1 (0.7%)	0 (0.0%)	0.403

IQR interquartile range, *LOS* length-of-stay, *ICU* intensive care unit, *MT* massive transfusion, *UR* unbalanced ratio (> 2:1 PRBC:Plasma), *BR* balanced ratio (≤ 2:1 PRBC:Plasma), *ARDS* acute respiratory distress syndrome, *CVA* Cerebrovascular accident, *CRBSI* Catheter-related bloodstream infection, *OR* Operating room, *CAUTI* Catheter-associated urinary tract infection, *CLASBI* central line-associated bloodstream infection.

Cunningham 2019

Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1

Table 2 – Twenty-four hours Plasma:RBC ratio outcomes.

	Low <1:2 (*n* = 163)	Medium ≥1:2 to <1:1 (*n* = 176)	High ≥1:1 (*n* = 126)	*P*
Acute kidney injury	0 (0)	4 (2)	3 (2)	0.10
ARDS	1 (1)	3 (2)	1 (1)	0.74
DVT/PE	5 (3)	5 (3)	8 (6)	0.26
Infection	16 (10)	23 (13)	23 (18)	0.12
Severe sepsis	1 (1)	2 (1)	0 (0)	0.78

Data presented as either median [IQR] or *n* (%).
Volume in milliliter per kilogram (mL/kg).
ARDS = acute respiratory distress syndrome; DVT = deep venous thrombosis; PE = pulmonary embolism.

Nederpelt 2019

Different FFP:pRBC ratios (patients were assigned to 7 ratio cohorts (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, and over 1:6 [1:6+]). Infectious complications (surgical site infections [SSIs], ventilator associated pneumonia, sepsis, extremity compartment syndrome, acute respiratory distress syndrome [ARDS]). When unadjusted outcomes were compared (Table 3), the 1:1 ratio cohort had the highest incidence of urinary tract infections (3.9%, p = 0.011), organ space surgical site infections (3.8%, p = 0.004), sepsis (5.0%, 0.019), acute kidney injuries (13.4%, p < 0.0001), and unplanned reoperations (8.41%, p < 0.0001).

Variable	1: 1	1: 2	1: 3	1: 4	1: 5	1: 6	1: 6+	p Value	p < 0.05 on multivariable regression
VAP, n (%)	159 (11.42)	195 (10.83)	42 (8.54)	13 (6.84)	5 (6.33)	1 (1.96)	37 (8.77)	0.045	No
ARDS, n (%)	77 (5.53)	89 (4.94)	17 (3.46)	10 (5.26)	1 (1.27)	1 (1.96)	18 (4.27)	0.316	No
Superficial SSI, n (%)	30 (2.16)	38 (2.11)	11 (2.24)	5 (2.63)	0	1 (1.96)	7 (1.66)	0.875	No
Deep SSI, n (%)	43 (3.09)	65 (3.55)	9 (1.83)	3 (1.58)	0	0	9 (2.13)	0.092	No
Organ space SSI, n (%)	53 (3.81)	50 (2.78)	6 (1.22)	0	1 (1.27)	0	8 (1.90)	0.004	No
Sepsis, n (%)	69 (4.96)	85 (4.72)	11 (2.24)	5 (2.63)	1 (1.27)	0	12 (2.82)	0.019	No
CLABSI, n (%)	16 (1.15)	13 (0.72)	2 (0.41)	1 (0.53)	0	0	3 (0.71)	0.602	No
Osteomyelitis, n (%)	3 (0.22)	7 (0.39)	1 (0.20)	0	0	0		0.76	No
UTI, n (%)	54 (3.88)	68 (3.78)	8 (1.63)	7 (3.68)	0	0	6 (1.42)	0.011	No
AKI, n (%)	186 (13.36)	143 (7.94)	24 (2.88)	8 (4.21)	2 (2.53)	0	20 (4.74)	<0.0001	No
Extremity compartment syndrome, n (%)	40 (2.87)	29 (1.61)	8 (1.63)	1 (0.53)	2 (2.53)	2 (3.92)	8 (1.90)	0.117	No
Unplanned reoperation, n (%)	117 (8.41)	142 (7.88)	24 (4.88)	5 (2.63)	2 (2.53)	0	20 (4.74)	<0.0001	No

AKI, acute kidney injury; ARDS, adult respiratory distress syndrome; CLABSI, central line associated blood stream infection; LOS, length of stay; SSI, surgical site infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

5. Acute transfusion reaction

Pediatric population

Butler 2019

The patients were divided into three groups based on their FFP:PRBC ratio at 24h: low (<1:2), medium (≥1:2 and <1:1) and high (≥1:1). There were no transfusion reactions.

		FFP:PRBC		
	All massive transfusion	**Low <1:2**	**Med ≥1:2 & <1:1**	**High ≥1:1**
	n=583	n=232	n=215	n=136
Transfusion reaction	0 (0)	0 (0)	0 (0)	0 (0)

IMPORTANT OUTCOMES

1. ***Time to definitive control of haemorrhage***

Pediatric population

Cunningham 2019

Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1. Children who received a low ratio of plasma:RBC underwent fewer hemorrhage control procedures (Table 2). Logistic regression was performed controlling for clinically significant variables and variables with P < 0.1 on univariate analysis. Those who were older in age, had a higher GCS, and received greater total blood product were more likely to undergo a hemorrhage control procedure

Table 2 – Twenty-four hours Plasma:RBC ratio outcomes.

	Low <1:2 (n = 163)	Medium ≥1:2 to <1:1 (n = 176)	High ≥1:1 (n = 126)	P
Hemorrhage control procedure	56 (34)	98 (56)	63 (50)	<0.01

Table 4 – Odds of undergoing hemorrhage control procedure.

	AOR (95% CI)	P
24-h Plasma:RBC		
Low	0.4 (0.13-1.22)	0.10
Medium	1.1 (0.46-2.56)	0.86
*High	-	-
24-h Platelet:RBC		
Low	1.8 (0.28-11.17)	0.54
Medium	1.1 (0.15-8.03)	0.92
*High	-	-
Female	0.9 (0.62-2.29)	0.60
Penetrating injury	1.2 (0.62-2.29)	0.60
Age	1.1 (1.08-1.18)	<0.01
ISS	1.0 (0.97-1.02)	0.81
GCS	1.2 (1.06-1.18)	<0.01
†Total blood product	1.0 (1.01-1.00)	<0.01

* Reference.
† Volume in mL/kg.

2. ***Patient-reported outcomes: pain/discomfort return to normal activities psychological wellbeing)***

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Study	Design	Comparison	Mortality 24 hours	Mortality 30 days	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage
Luz 2019* *some studies had wrong intervention and/or comparator (adj and not)	SR	FFP:RBC 1:1 vs <1:1 FFP:RBC 1:1.5 vs <1:1.5 FFP:RBC 1:2 vs <1:2	5 observational studies 2414 participants: The random effects pooled OR 0.34 (95% confidence [CI] = 0.14–0.82; I2 = 88%, P < 0.01). 2 observational studies 118 participants: The random effects pooled OR 0.43 (95% confidence [CI] = 0.18–1.06; I2 = 0%, P =0.41). 6 observational studies 1388 participants: The random effects pooled OR 0.59 (95% confidence [CI] = 0.43–0.81; I2 = 22%, P =0.27).	10 observational studies 4203 participants: The random effects pooled OR 0.38 (95% confidence [CI] = 0.22–0.68; I2 = 91%, P <0.01). 5 observational studies 1369 participants: The random effects pooled OR 0.42 (95% confidence [CI] = 0.22–0.81; I2 = 73%, P =0.005). 10 observational studies 2849 participants: The random effects pooled OR 0.47 (95% confidence [CI] = 0.31–0.71; I2 = 81%, P <0.01).	no evidence	no evidence	no evidence	no evidence
Rahouma 2016* *some studies had wrong intervention and/or comparator (adj and not)	SR	FFP:RBC <1:1 vs ≥1:1 FFP:RBC <1:1.5 vs ≥1:1.5 FFP:RBC <1:2 vs ≥1:2	6 observational studies and 1 RCT 5265 participants: The random effects pooled OR 2.05 (95% confidence [CI] = 1.55–2.71; I2 = 57%, P = 0.03). 4 observational studies 1877 participants: The random effects pooled OR 3.97 (95% confidence [CI] = 1.37–11.49; I2 = 88%, P <0.01). 9 observational studies 3540 participants: The random effects pooled OR 2.85 (95% confidence [CI] = 2.14–3.81; I2 = 59%, P =0.01).	5 observational studies and 2 RCTs 5266 participants: The random effects pooled OR 1.36 (95% confidence [CI] = 1.09–1.69; I2 = 45%, P =0.09). 5 observational studies 1813 participants: The random effects pooled OR 2.45 (95% confidence [CI] = 1.14–5.25; I2 = 87%, P <0.01). 14 observational studies 6193 participants: The random effects pooled OR 1.77 (95% confidence [CI] = 1.50–2.10; I2 = 37%, P =0.08).	no evidence	**Acute respiratory distress syndrome** Six observational studies and two RCTs (Holcomb 2015; Nascimento 2013 with wrong intervention and/or comparator) OR: 0.68, CI 0.40-1.16, P = 0.16. **Acute lung injury** An observational study and one RCT (Holcomb 2015 with wrong intervention and/or comparator) OR: 1.23, CI 0.81-1.86, P = 0.34	no evidence	no evidence
Wirtz 2020 (unadj)	SR	1-2:2 (high ratio) vs <1:2 (low ratio)	no evidence	no evidence	no evidence	**Thromboembolic events** Two observational studies and one RCT (Holcomb 2015 with wrong intervention and/or comparator): OR, 1.34; 95% CI, 0.28-1.56; p = 0.34.	no evidence	no evidence
Overlapping of the studies included in the systematic reviews								
Luz 2019, Rodriguez	SR	FFP:RBC 1:1 vs <1:1	7 observational studies 4458 participants:	8 observational studies 5224 participants:	no evidence	no evidence	no evidence	no evidence

2020 and Rahouma 2016 (adj and not)		 FFP:RBC 1:1.5 vs < 1:1.5 FFP:RBC 1:2 vs <1:2	The random effects pooled OR 0.49 (95% confidence [CI] = 0.30–0.78; I2 = 80%, P < 0.01). 7 observational studies 2072 participants: The random effects pooled OR 0.32 (95% confidence [CI] = 0.17–0.63; I2 = 76%, P <0.01). 12 observational studies 4205 participants: The random effects pooled OR 0.52 (95% confidence [CI] = 0.34–0.79; I2 = 84%, P <0.01).	The random effects pooled OR 0.61 (95% confidence [CI] = 0.37–0.98; I2 = 87%, P < 0.01). 8 observational studies 2369 participants: The random effects pooled OR 0.45 (95% confidence [CI] = 0.27–0.74; I2 = 72%, P <0.01). 15 observational studies 4194 participants: The random effects pooled OR 0.54 (95% confidence [CI] = 0.40–0.72; I2 = 72%, P <0.01).				
Subgroup analysis: patients with Traumatic Brain Injury								
Haltmeier 2018	OBS	Plasma:PRBC <1 ≥1	 40 survived (46.5%)/46 died (53.5%) 103 survived (66%)/53 died (34%)	no evidence	no evidence	no evidence	no evidence	no evidence

Study	Design	Comparison	Mortality 24 hours	Mortality 30 days	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage
Pediatric populations: Pooled of the studies								
Sehdev 2020 Cannon 2017 (adj)	OBS	PRBC: plasma > 2:1 (Unbalanced) vs ≤ 2:1 (Balanced) Low (<1:2) and high (≥1:2) ratios of PLAS/PRBC	 2 observational studies, 603 patients: The random effects pooled aRR 1.53 (95% confidence [CI] = 0.84–2.77; I2 = 0%, P =0.16).	no evidence	no evidence	no evidence	no evidence	no evidence
Butler 2019 (adj)	OBS	FFP:PRBC: low (<1:2), medium (≥1:2 & <1:1), and high (≥1:1)	583 patients: High vs low: aRR 0.49 (95% confidence [CI] = 0.27–0.89). Medium vs low: aRR 0.60 (95% confidence [CI] = 0.39–0.92).					
Butler 2019 Cunningham 2019 (unadj)	OBS	FFP:PRBC: low (<1:2), medium (≥1:2 & <1:1), and high (≥1:1) Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1	no evidence	no evidence	no evidence	**Acute respiratory distress syndrome** 2 observational studies, 1048 patients: The random effects pooled aRR 2.09 (95% CI 0.70-6.23) and I2=0%, P=0.77.	no evidence	no evidence
Sehdev 202	OBS	PRBC: plasma > 2:1 (Unbalanced) vs ≤ 2:1	no evidence	no evidence	no evidence	**Acute respiratory distress syndrome**	no evidence	no evidence

(unadj)		(Balanced)				245 patients: The aOR 0.71 (95% CI 0.13-3.97).		
Sehdev 2020 (adj)	OBS	severely UR of ≥ 4:1 PRBC: plasma vs BR of ≤ 2:1 PRBC: plasma of > 2:1 (Unbalanced) vs ≤ 2:1 (Balanced)	n=98 UR and n=141 BR aOR 1.42 CI 0.53–3.80, p = 0.489 **1–12 years** old (n = 90) aOR 1.71, CI 0.65–4.50, p = 0.277. **13-to-17 years** old (n = 149) aOR 1.58, CI 0.60–4.16, p = 0.351. **Blunt trauma**: BR 29/141 (48.3%) vs UR 25/98 (5.6%) **Penetrating trauma**: BR 12/141 (41.4%) vs 7/98 (46.7%)	no evidence	ICU days, median (IQR): BR n=131, 5(13), UR n=98, vs UR 4(11)	no evidence	no evidence	no evidence
Nederpelt 2019 (adj)	OBS	FFP:pRBC ratios: 1:2 (n=1801) vs 1:1 (n=1392) 1:3 (n=492) vs 1:1 1:4 (n=190) vs 1:1 1:5 (n=79) vs 1:1 1:6 (n=51) vs 1:1 1:6 [1:6+] (n=422) vs 1:1	aOR 1.23 (95% CI 1.02-1.48) aOR 1.62 (95% CI 1.24-2.11) aOR 2.11 (95% CI 1.42-3.13) aOR 4.11 (95% CI 2.31-7.31) aOR 2.98 (95% CI 2.31-6.13) aOR 1.25 (95% CI 0.94-1.67)	no evidence	ICU LOS, mean (SD) 1:1; 12 (13) 1:2; 12 (15) 1:3; 10 (11) 1:4; 10 (13) 1:5; 7 (7) 1:6; 10 (12) 1:6+, 10 (11)	ARDS, n (%) 1:1, 77 (5.53) 1:2, 89 (4.94) 1:3, 17 (3.46) 1:4, 10 (5.26) 1:5, 1 (1.27) 1:6, 1 (1.96) 1:6+, 18 (4.27)	no evidence	no evidence
Cannon 2017	OBS	Low (<1:2) and high (≥1:2) PLAS/PRBC 1:2	no evidence	no evidence	ICU free days, median (IQR): Low ratio n=65, 24 (16-26); High ratio n=299, 22 (14-26)	no evidence	no evidence	no evidence
Butler 2019	OBS	FFP:PRBC: low (<1:2), medium (≥1:2 and <1:1) and high (≥1:1)	no evidence	no evidence	ICU length of stay, median (IQR): Low n=128, 12 (6-18); Med n=118, 10 (5-20); High n=90, 13 (7-18)	Any complications n (%): Low n=232, 28 (12.1); Med n=215, 39 (18.1); High n=136, 26 (19.1)	No transfusion reactions in either groups.	no evidence
Cunningham 2019 (adj)	OBS	Plasma:RBC: low <1:2, medium ≥1:2 to <1:1, and high ≥1:1	no evidence	no evidence	ICU free days, median (IQR): Low n=163, 7 (0-19); Med n=176, 2 (0-21); High n=126, 12 (0-20)	no evidence	no evidence	Hemorrhage control procedure: Low n=163, 56 (34); Med n=176, 98 (56); High n=126, 63 (50). Low vs High ratio: aOR 0.4 (95% CI 0.13-1.22) Med vs High aOR 1.10 (95% CI 0.46-2.56)
Pediatric patients with Traumatic Brain Injury								
Cannon 2017 (adj)	OBS	Low (<1:2) and high (≥1:2) of PLAS/PRBC 1:2	286 participants aOR 1.06 (95% CI 0.47-2.39).	no evidence	no evidence	no evidence	no evidence	no evidence

C3- Platelets: Red Blood Cell Ratios

Gli outcome riportati tra le revisioni sistematiche individuate sono riportati in tabella:

Author - year	Study design	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological
General population								
Balvers 2012	Observational study, from Luz 2019 SR							
Brown 2012	Observational study, from Luz 2019 SR							
Cap 2012	Observational study, from Wirtz 2019 SR							
Haltmeier 2017	Observational study, from Luz 2019 SR							
Holcomb 2011	Observational study, from Luz 2019 SR							
Holcomb 2013	Observational study, from Luz 2019 SR							
Perkins 2009	Observational study, from Luz 2019 SR							
Sambasivan 2011	Observational study, from Luz 2019 SR							
Sharpe 2012	Observational study, from Luz 2019 SR							
Shaz 2010	Observational study, from Luz 2019 SR							
Spinella 2011	Observational study, from Luz 2019 SR							
Pediatric population								
Butler 2019	Observational study, from search strategy Pediatric population							
Cunningham 2019	Observational study, from search strategy Pediatric population							

CRITICAL OUTCOMES

Si riporta di seguito la sintesi descrittiva dei risultati dei singoli studi.

1. Mortality at 24 hours, 30days/1 month, and 12 months

Le misurazioni sono eterogenee nelle comparazioni, pertanto non è possibile presentare una stima aggregata. Per comparazioni e rapporti specifici di interesse si rimanda al singolo studio.

Mortality at 24 hours

Author - year	Study design	Mortality at 24 hours
Balvers 2018	Observational study, from Luz 2019 SR	HIGH (≥1:1) vs LOW (<1:1) **Survival and free of massive transfusion:** OR 2.67 (1.24 – 5.77)
Brown 2012	Observational study, from Luz 2019 SR	HIGH (≥1:9) vs LOW (<1:9) **Mortality:** - PLT:PRBC ratio within 6 h: HR 0.34 (0.11 – 0.89) - PLT:PRBC ratio within 12 h: HR 0.17 (0.04 – 0.54) - PLT:PRBC ratio within 24 h: HR 0.26 (0.06 – 0.86)
Cap 2012	Observational study, from Wirtz 2019 SR	HIGH (≥0.1) vs LOW (≤0.1) **Survival:** HR 4.25 (1.25 – 14.48)
Holcomb 2011	Observational study, from Luz 2019 SR	LOW (> 1:20) vs HIGH (1:1) **Mortality:** RR 2.81 (1.36 – 5.8) MEDIUM (1:2) vs HIGH (1:1) **Mortality:** RR 3.13 (1.52 – 6.45)
Perkins 2009	Observational study, from Luz 2019 SR	HIGH (1:8), MEDIUM (1:16 to 1:8), LOW (< 1:16) **Mortality:** OR 0.82 (0.72 – 0.93)
Butler 2019	Observational study, from search strategy. Pediatric population	HIGH (≥1:1) vs NONE (0) **Mortality:** - PLT:PRBC ratio within 4 h: RR 1.73 (0.90 – 3.34) - PLT:PRBC ratio within 24 h: RR 1.04 (0.52 – 2.09) LOW (>0 and <1:2) vs NONE (0) **Mortality:** - PLT:PRBC ratio within 4 h: RR 1.81 (1.11 – 2.94) - PLT:PRBC ratio within 24 h: RR 1.29 (0.81 – 2.05) CONTINUOUS **Mortality:** - PLT:PRBC ratio within 4 h: RR 1.53 (0.84 – 2.77) - PLT:PRBC ratio within 24 h: RR 0.94 (0.51 – 1.71)

In-hospital mortality

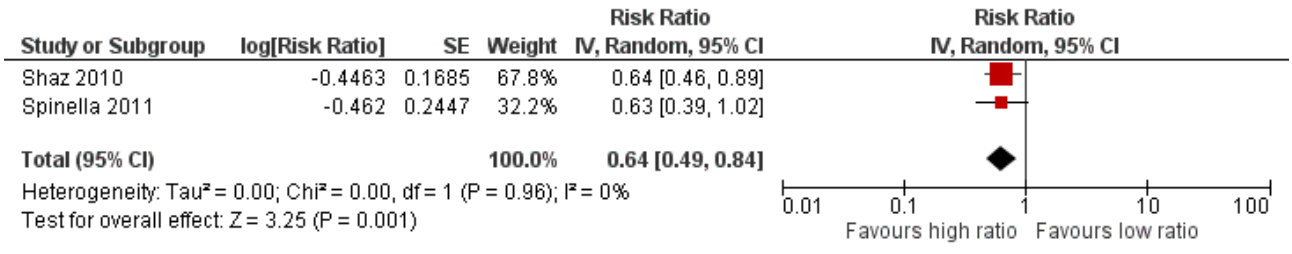
Author - year	Study design	In-hospital mortality
Haltmeier 2017	Observational study, from Luz 2019 SR	HIGH (≥1) vs LOW (<1) **Mortality:** OR 0.39 (0.08 – 1.92)
Holcomb 2013	Observational study, from Luz 2019 SR	HIGH (≥1:1) vs LOW (<1:2) **Mortality:** - early PLT:PRBC ratio: OR 0.37 - PLT:PRBC ratio within 6 h: OR 0.49 - PLT:PRBC ratio within 24 h: OR 0.69

		MEDIUM (≥1:2, <1:1) vs LOW (<1:2) **Mortality:** - early PLT:PRBC ratio: OR 0.66 - PLT:PRBC ratio within 6 h: OR 0.79 - PLT:PRBC ratio within 24 h: OR 1.23 CONTINUOUS **Mortality:** - early PLT:PRBC ratio: OR 0.55 (0.31 – 0.98) - PLT:PRBC ratio within 6 h: OR 0.81 (0.46 – 1.43) - PLT:PRBC ratio within 24 h: OR 0.78 (0.57 – 1.06)
Sambasivan 2011	Observational study, from Luz 2019 SR	HIGH (≥1:1) vs LOW (<1:1) **Mortality:** RR 1.03 (0.55 – 1.92) HIGH (≥1:2) vs LOW (<1:2) **Mortality:** RR 0.65 (0.30 – 1.42)
Sharpe 2012	Observational study, from Luz 2019 SR	LOW (<0.33) vs HIGH (>0.5) **Mortality:** RR 1.92 (0.99 – 3.71) MEDIUM (0.33 – 0.5) vs HIGH (> 0.5) **Mortality:** RR 1.32 (0.55 – 3.12)
Butler 2019	Observational study, from search strategy. Pediatric population	CONTINUOUS **Mortality:** RR 1.17 (0.91 – 1.50)

Mortality at 30 days

Author - year	Study design	Mortality at 30 days
Cap 2012	Observational study, from Wirtz 2019 SR	HIGH (≥0.1) vs LOW (≤0.1) **Survival:** HR 2.32 (1.11 – 4.84)
Holcomb 2011	Observational study, from Luz 2019 SR	LOW (> 1:20) vs HIGH (1:1) **Mortality:** RR 1.77 (1.16 – 2.68) MEDIUM (1:2) vs HIGH (1:1) **Mortality:** RR 1.75 (1.15 – 2.65)
Perkins 2009	Observational study, from Luz 2019 SR	HIGH (1:8), MEDIUM (1:16 to 1:8), LOW (< 1:16) **Mortality:** OR 0.91 (0.86 – 0.95)
Shaz 2010	Observational study, from Luz 2019 SR	HIGH (≥1:1, 1:1 – 1:2) vs LOW (<1:2, 0) **Survival:** OR 1.55 (1.09 – 2.18)
Spinella 2011	Observational study, from Luz 2019 SR	HIGH (≥1:2) vs LOW (<1:2) **Mortality:** - Non TBI patient: HR 0.63 (0.39 – 0.86) - TBI patient: HR 0.47 (0.27 – 0.82)

Per i risultati derivanti dagli studi osservazionali di Shaz 2010 e Spinella 2011, che considerano lo stesso ratio nel gruppo "low" (<1:2), e ratio simili nel gruppo "high" (≥1:2), è stata prodotta una stima pooled per la mortalità a 30 giorni. Dal grafico emerge una diminuzione significativa della mortalità a 30 giorni del 36% nel gruppo di pazienti a cui è stata somministrata una dose "high" di PLT:PRBC rispetto al gruppo a cui è stata somministrata una dose "low".



2. Health related quality of life

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

3. Length of intensive care stay

Author - year	Study design	Length of intensive care stay
Brown 2012	Observational study, from Luz 2019 SR	HIGH (≥1:9) vs LOW (<1:9) **LOS [Mean (SD)]:** High: 30.1 (35), Low 25.3 (29) **ICU LOS [Mean (SD)]:** High: 18.2 (18), Low 14.8 (15)
Holcomb 2011	Observational study, from Luz 2019 SR	LOW (> 1:20), MEDIUM (1:2), HIGH (1:1) **Hospital free days [mean (SD)]:** Low 4 (8), Medium 4 (7), High: 5 (7) **ICU free days [mean (SD)]:** Low 8 (11), Medium 9 (11), High: 10 (11) **Ventilator free days [mean (SD)]:** Low 7 (11), Medium 9 (12), High: 10 (12)
Sambasivan 2011	Observational study, from Luz 2019 SR	LOW (<1:1), HIGH (≥1:1) **Hospital free days [median (IQR)]:** Low 17 (0-24), High: 13 (0-22) **ICU free days [median (IQR)]:** Low 25.5 (9-29), High: 20 (0-27) **Ventilator free days [median (IQR)]:** Low 27 (0-30), High: 15 (0-28) LOW (<1:2), HIGH (≥1:2) **Hospital free days [median (IQR)]:** Low 17 (0-24), High: 11 (0-21) **ICU free days [median (IQR)]:** Low 26 (10-29), High: 19 (3-27) **Ventilator free days [median (IQR)]:** Low 27 (0-30), High: 7 (0-26)
Cunningham 2019	Observational study, from search strategy. Pediatric population	LOW (<1:2), MEDIUM (≥1:2), HIGH (≥1:1) **Hospital free days [median (IQR)]:** Low 0 (0-11), Medium 0 (0-10), High: 0 (0-15) **ICU free days [median (IQR)]:** Low 8 (0-21), Medium 9 (0-17), High: 7 (0-21) **Ventilator free days [median (IQR)]:** Low 12 (0-23), Medium 11 (0-21), High: 14 (0-25)
Butler 2019	Observational study, from search strategy. Pediatric population	CONTINUOUS higher vs lower **Hospital free days:** RR 7.02 (0.04 – 1250) **ICU free days:** RR 1.92 (0.05 – 69.53) **Ventilator free days:** RR 0.77 (0.02 – 35.37)

4. Adverse effects

Author - year	Study design	Length of intensive care stay
Brown 2012	Observational study, from Luz 2019 SR	HIGH (≥1:9) vs LOW (<1:9) **MOF:** HR 1.06 **ARDS:** HR 1.11
Butler 2019	Observational study, from search strategy. Pediatric population	CONTINUOUS higher vs lower **ANY:** RR 0.96 (0.69 – 1.34) **ARDS:** HR 0.34 (0.02 – 7.24)

Si riportano, di seguito:

- le diverse complicazioni presenti nello studio osservazionale di Butler 2019, relativo alla popolazione pediatrica.

Secondary Outcomes	Fresh Frozen Plasma:PRBC Ratio aRR (95% CI)	Platelet:PRBC Ratio aRR (95% CI)
Complications		
Any	1.05 (0.80–1.38)	0.96 (0.69–1.34)
Deep vein thrombosis	1.77 (1.22–2.57)	0.17 (0.02–1.30)
Pneumonia	1.10 (0.49–2.47)	1.94 (1.14–3.28)
Unplanned return to operating room	1.07 (0.28–4.08)	1.07 (0.28–4.08)
Acute respiratory distress syndrome	1.29 (0.69–2.41)	0.34 (0.02–7.24)
Unplanned ICU admission or return to ICU	1.41 (0.71–2.77)	0.20 (0.01–3.95)
Acute kidney injury	0.85 (0.25–2.85)	1.78 (0.54–5.91)
Unplanned intubation	0.45 (0.10–2.07)	1.97 (0.37–10.52)
Stroke	1.44 (0.67–3.08)	1.11 (0.31–4.03)
Severe sepsis	0.24 (0.02–2.83)	0.96 (0.19–4.82)
Extremity compartment syndrome	1.19 (0.45–3.16)	2.64 (0.09–76.0)
Pulmonary embolism	0.53 (0.04–7.22)	1.31 (0.13–13.4)

- le diverse complicazioni presenti nello studio osservazionale di Cunningham 2019, relativo alla popolazione pediatrica, per cui, tuttavia, non è stata riportata una stima.

Table 3 — Twenty-four hours Platelet:RBC ratio outcomes.

	Low <1:2 ($n = 376$)	Medium ≥1:2 to <1:1 ($n = 64$)	High ≥1:1 ($n = 25$)	P
Acute kidney injury	5 (1)	2 (3)	0 (0)	0.51
ARDS	6 (3)	4 (3)	8 (7)	0.19
DVT/PE	17 (5)	0 (0)	1 (4)	0.21
Infection	48 (13)	10 (16)	4 (16)	0.66
Severe sepsis	2 (1)	1 (2)	0 (0)	0.47

5. Acute transfusion reaction

L'outcome di interesse è riportato per la sola popolazione pediatrica nello studio di Butler 2019, da cui non emergono reazioni acute alla trasfusione in nessuno dei due gruppi ("high" e "low").

IMPORTANT OUTCOMES

1. Time to definitive control of haemorrhage

Per l'outcome di interesse, si riporta, di seguito, quanto emerso dallo studio osservazionale di Cunningham 2019, relativo alla popolazione pediatrica.

Table 4 – Odds of undergoing hemorrhage control procedure.

	AOR (95% CI)	P
24-h Plasma:RBC		
Low	0.4 (0.13-1.22)	0.10
Medium	1.1 (0.46-2.56)	0.86
*High	-	-
24-h Platelet:RBC		
Low	1.8 (0.28-11.17)	0.54
Medium	1.1 (0.15-8.03)	0.92
*High	-	-
Female	0.9 (0.62-2.29)	0.60
Penetrating injury	1.2 (0.62-2.29)	0.60
Age	1.1 (1.08-1.18)	<0.01
ISS	1.0 (0.97-1.02)	0.81
GCS	1.2 (1.06-1.18)	<0.01
†Total blood product	1.0 (1.01-1.00)	<0.01

*Reference.
†Volume in mL/kg.

2. Patient-reported outcomes: pain/discomfort return to normal activities psychological wellbeing)

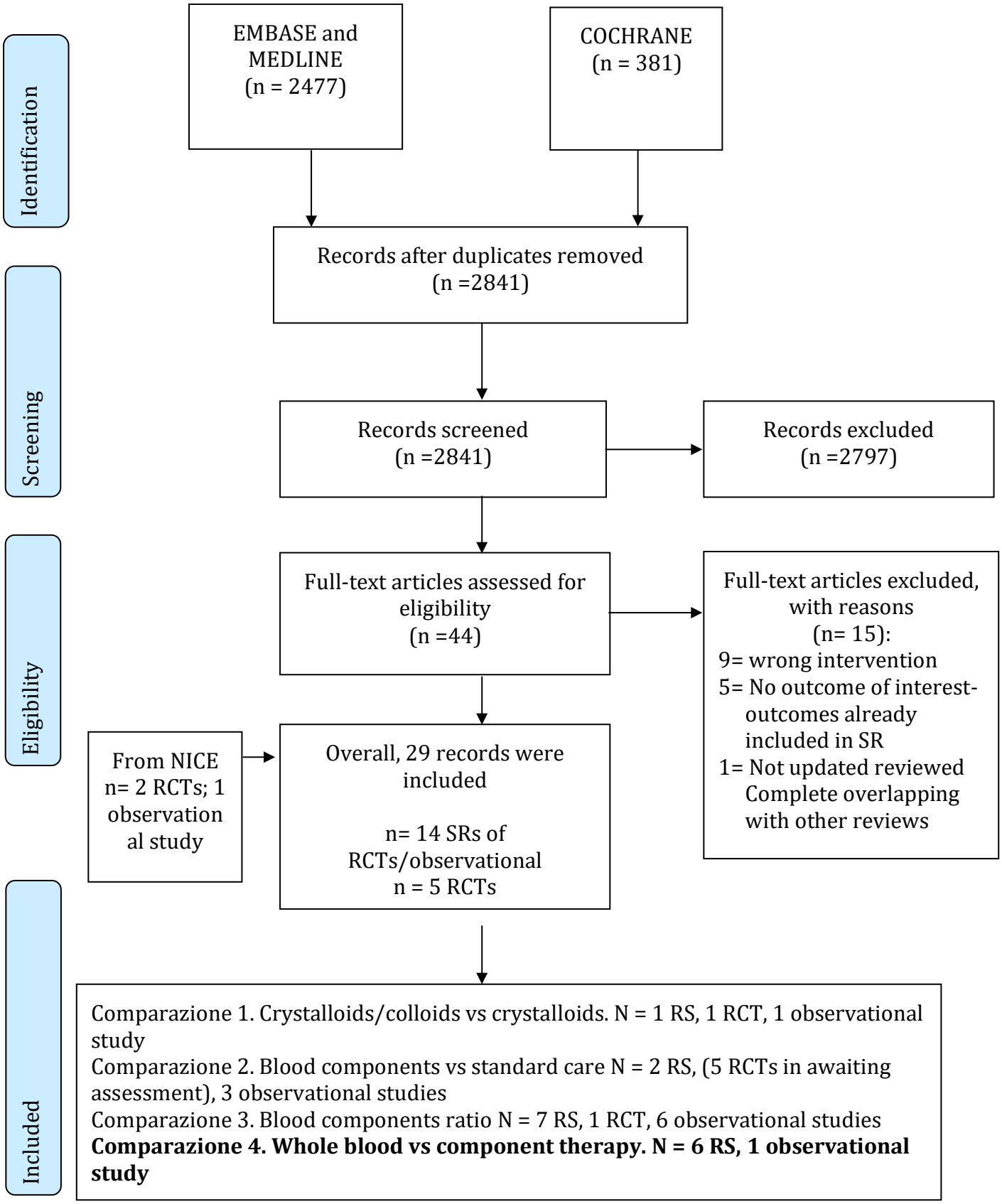
Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Appendice C4 – Comparazione: Whole Blood vs Component therapy

INDICE

SELEZIONE DEGLI STUDI

Figure 1. Flow Chart of study selection



OUTCOME

E' stata effettutata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono state individuate 6 SR e 1 studio osservazionale che permettono di rispondere alla seguente comparazione includendo gli outcome critici e importanti. Inoltre le RS hanno in comune uno studio randomizzato e controllato con outcome agiguntivi.

- *Whole blood vs Component therapy*

Gli outcome riportati tra gli studi primari (1 RCT e 1 studio osservazionale) e le revisioni sistematiche individuate sono riportati in tabella:

Author - year	Study design	Trials assessing the comparisons whole blood vs component therapy	Mortality at 24 hours, 30 days/1month and 12 months	Health related quality of life	Length of intensive care stay	Adverse effects	Acute transfusion reaction	Time to definitive control of haemorrhage	Patient-reported outcomes: return to normal activities psychological
McQuilten 2020	SR (quantitative synthesis)	1 RCT (Cotton 2013)							
Crowe 2020	SR (quantitative synthesis)	1 RCT(Cotton 2013), 11 observational							
Avery 2020	SR (qualitative synthesis)	1 RCT(Cotton 2013), 5 observational							
Cruciani 2020	SR (quantitative synthesis)	1 RCT (Cotton 2013), 6 observational							
Malkin 2020	SR (qualitative synthesis)	1 RCT (Cotton 2013), 4 observational							
Ritchie 2020	SR (qualitative synthesis)	1 RCT (Cotton 2013)							
Cotton 2013	RCT								
Leeper 2020	Observational (children)								

CRITICAL OUTCOMES

13. Mortality at 24 hours, 30days/1 month, and 12 months

Sei revisioni sistematiche includono l'outcome di interesse. Si riporta di seguito la sintesi descrittiva dei risultati.

Author - year	Study design	Trials assessing the comparisons whole blood vs component therapy	Mortality at 24 hours, 30 days/1month and 12 months
McQuilten 2020	SR	1 RCT(Cotton 2013) 107 participants	**Mortality 24 h** RR 1.13 (0.37-3.49), Anticipated absolute effects control 96 per 1000, intervention 12 more per 1000 (61 fewer to 239 more). Certainty of evidence VERY LOW **Mortality 30 days** RR 1.42 (0.63-3.19), Anticipated absolute effects control 154 per 1000, intervention 65 more per 1000 (57 fewer to 337 more). Certainty of evidence VERY LOW
Crowe 2020	SR	1 RCT(Cotton 2013), 11 observational	**Mortality 24 h** The fixed effects pooled OR 0.83 (95% confidence [CI] = 0.56–1.24). For 24-hour mortality, there was a small to moderate level of heterogeneity (I2 = 27.2%, P = 0.37) (Figure 2). **Mortality 30 days** The DerSimonian and Laird random effects pooled OR for in-hospital/30-day mortality was 0.79 (95% CI = 0.49–1.31). Moderate to high degree of heterogeneity (I^2 = 87.3%, P = 0.37).
Avery 2020	SR	1 RCT(Cotton 2013), 5 observational	Qualitative synthesis
Cruciani 2020	SR	1 RCT (Cotton 2013), 6 observational	**Mortality 24 h** were available from three studies (one RCT and two cohort studies). Twenty-four hour mortality did not differ significantly between WB and COMP recipients (OR 0.80; 95% CIs 0.40/1.59; p = 0.53; I2 = 56%) (Fig. 4). The results were much the same when the analyses were limited to observational studies alone for 24-h mortality, OR 0.84; 95% CIs 0.33/2.15. **Mortality 30 days** Thirty-day/in-hospital mortality was available from one RCT and six cohort studies. The effect size did not differ between WB and COMP recipients (OR 0.90: 95 CIs 0.62/1.30; p = 0.56: I2 = 56%). - The results were much the same when the analyses were limited to observational studies alone (for 30-day/in-hospital mortality, OR 0.82; 95% CIs 0.56/1.20). In the RCT the OR for 30-days mortality was 1.81 (95% CIs 0.80/4.09; p = 0.15). - After adjustment for baseline covariates, the OR for mortality was significantly lower in WB recipients compared to COMP (OR 0.22; 95% CIs 0.10/0.45); p < 0.001; I2 = 12). - 30-day/in-hospital mortality adjusted HR was not statistically significant between groups (HR, 0.72; 95% CIs 0.45/1.16; p = 0.176; I2 = 0). - 30-day crude mortality was higher in civilian than in military setting (27.5% versus 17.4%; p < 0.0001), independently of the type of transfusion (WB or COMP), but probably in relation to the older age and prevalence of chronic conditions in civilian setting.
Malkin 2020	SR	1 RCT (Cotton 2013), 4 observational	Qualitative synthesis
Ritchie 2020	SR	1 RCT (Cotton 2013)	Qualitative synthesis

McQuilten 2020

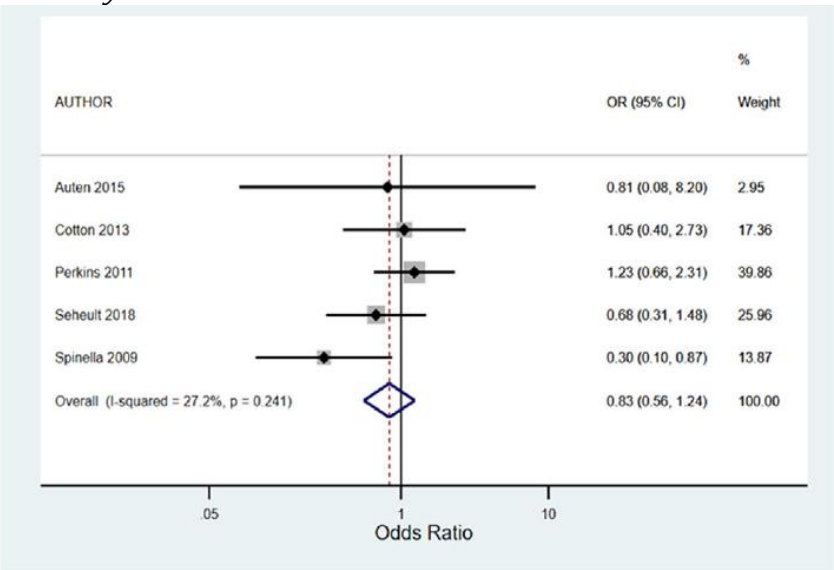
La revision sistematica McQuilten 2020 riporta l'outcome mortalità a 24 ore e 30 giorni. I dati provengono da un unico studio randomizzato e controllato, Cotton et al. 2013. Di seguito si riporta la tabella delle evidenze con relativa valutazione della qualità.

Table 3
GRADE quality assessment and summary of findings table

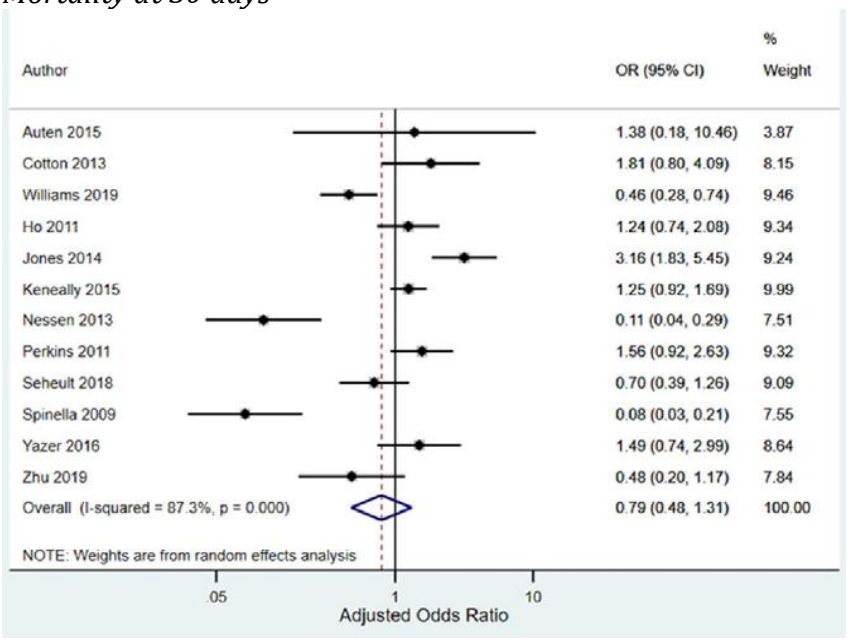
Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) Control	Intervention	Relative effect (95% CI)	Anticipated absolute effects Control	Intervention
Whole blood vs component therapy: Mortality – 24 h											
107 (1 RCT)	Very Serious	Not serious	Not serious	Very Serious	None	⊕◯◯◯ VERY LOW	5/52 (9.6%)	6/55 (10.9%)	RR 1.13 (0.37-3.49)	96 per 1000	12 more per 1000 (61 fewer to 239 more)
Whole blood vs component therapy: Mortality – 30 d											
107 (1 RCT)	Very Serious	Not serious	Not serious	Very Serious	None	⊕◯◯◯ VERY LOW	8/52 (15.4%)	12/55 (21.8%)	RR 1.42 (0.63-3.19)	154 per 1000	65 more per 1000 (57 fewer to 337 more)

Crowe 2020

Mortality at 24 h



Mortality at 30 days



Avery 2020
Only qualitative synthesis no cumulative data.

Cruciani 2020

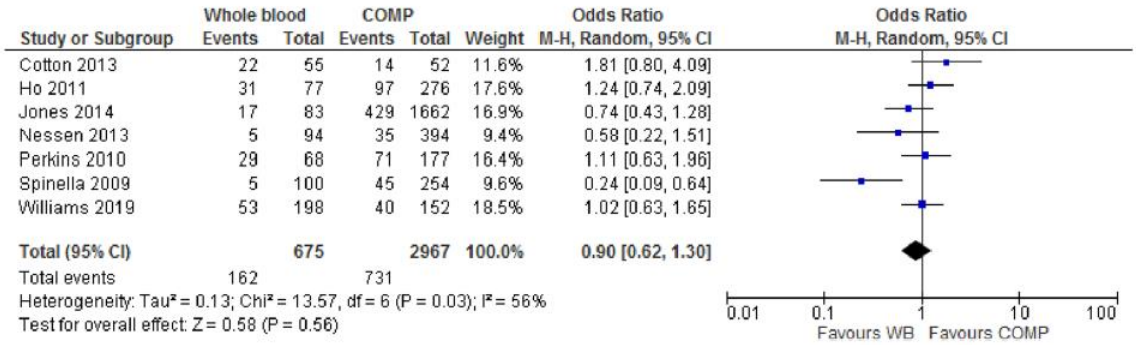


Fig. 3 Forest plot of comparison (whole blood versus blood component transfusion) of 30-day/in-hospital mortality

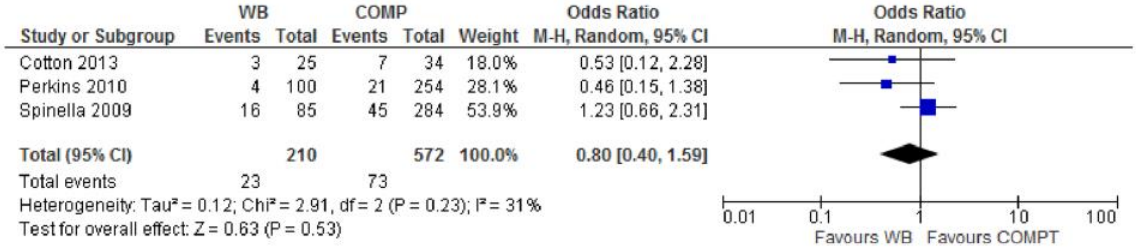
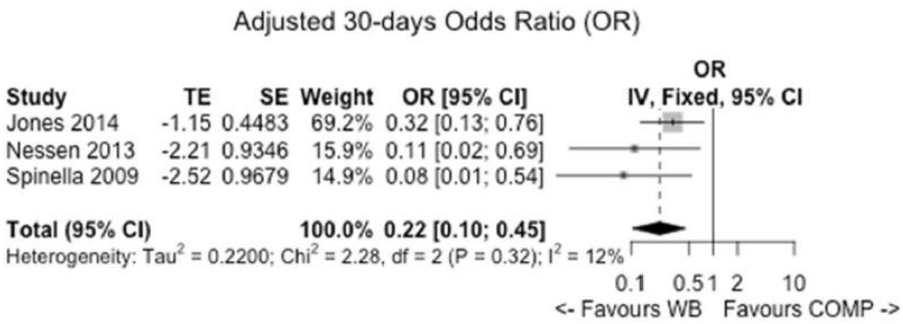


Fig. 4 Forest plot of comparison (whole blood versus blood component transfusion) of 24-h mortality

Fig. 5 Forest plot of whole blood effect on 30 days/ in-hospital mortality (adjusted odds ratio). Inverse-variance, fixed effect pooling of adjusted OR from multiple logistic regression. TE is treatment effect as log OR at study level; SE is the standard error. The summary measure is expressed as OR



Malkin 2020
Only qualitative synthesis no cumulative data.

Ritchie 2020
Only qualitative synthesis no cumulative data.

Subgroup Children

Leeper 2020: subgroup CHILDREN – observational study
Tra le prove disponibili, uno studio osservazionale-propensity-matched cohort (Leeper 2020) condotto sui bambini affetti da trauma maggiore riporta l'outcome di interesse.
Regarding additional clinical outcomes, there was no difference in rate of in-hospital death, functional disability, hospital LOS, ICU LOS, and ventilator days between the 2 groups (Table 2; all P > 0.25).

TABLE 2. Outcome Measures Between LTOWB and Component Recipients

	LTOWB	Components	*P*-value
Outcomes			
Mortality	8/28 (29%)	12/28 (43%)	0.40
Functional disability (survivors)	12/21 (57%)	8/16 (50%)	0.75
Hospital length of Stay median (IQR)	8 (1–18)	8 (4–13)	0.74
ICU length of stay median (IQR)	4 (2–7)	3 (1–9)	0.89
Ventilator days median (IQR)	2 (0–5)	1 (0–6)	0.8

ICU indicates intensive care unit; IQR, interquartile range; LTOWB, low titer group O whole blood.

14. Health related quality of life

Subgroup children

Tra le prove disponibili, uno studio osservazionale-propensity-matched cohort (Leeper 2020) condotto sui bambini affetti da trauma maggiore riporta l'outcome di interesse.
Lo studio valuta l'efficacia in termini di "funciontal disability" definita come "functional disability at discharge (defined by a functional independence measure score of dependent in any category or discharge to a rehabilitation facility)" in 28 bambini sottoposti a Low Titer Group O Whole Blood Transfusion Protocol e 28 bambini a component therapy.

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ICU indicates intensive care unit; IQR, interquartile range; LTOWB, low titer group O whole blood.

15. Length of intensive care stay

Cotton 2013
Lo studio randomizzato e controllato (Cotton et al. 2013) riporta l'outcome di interesse.
When comparing length of stay between WB and COMP subjects, there were no differences in:
- hospital-free days (median 15 days, 25th and 75th IQR of 4 and 23 vs 16 days, IQR of 7 and 23; P = 0.85),

- intensive care unit–free days (median 30 days, IQR of 11 and 30 vs 29 days, IQR of 17 and 30; P = 0.89),
- ventilator-free days (median 30 days, IQR of 26 and 30 vs 30 days, IQR of 26 and 30; P = 0.35).

Subgroup Children

Leeper 2020: subgroup Children

Tra le prove disponibili, uno studio osservazionale-propensity-matched cohort (Leeper 2020) condotto sui bambini affetti da trauma maggiore riporta l'outcome di interesse.

Regarding additional clinical outcomes, there was no difference in rate of in-hospital death, functional disability, hospital LOS, ICU LOS, and ventilator days between the 2 groups (Table 2; all P > 0.25).

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Ventilator days median (IQR)	2 (0–5)	1 (0–6)	0.8

ICU indicates intensive care unit; IQR, interquartile range; LTOWB, low titer group O whole blood.

16. Adverse effects

Tre revisioni sistematiche riportano l'outcome di interesse. Di seguito si riporta una tabella riassuntiva dei risultati.

Outcome	**Avery 2020** (Qualitative synthesis)	**Cruciani 2020** (Quantitative synthesis but qualitative for the outcome of interest)	**Malkin 2020** (Qualitative synthesis)
Acute respiratory distress syndrome	Three studies reported rates of ARDS. Two studies found no statistically significant difference between the two groups, and one study found a higher incidence of ARDS in the fresh WB group compared with apheresis platelets (aPLT) group (18.8% vs 7.4%, respectively, p=0.002).	One study reported a higher proportion of acute respiratory distress syndrome (ARDS), but not of multi-organ failure syndrome, infection, and embolic event, in WB recipients compared to COMP. (Perkins et al. 2011)	Perkins et al. reported a significantly higher rate of ARDS in the FWB group (18.8 vs 7.4, p = 0.002) and Spinella et al. showed a similar trend. The RCT by Cotton et al, did not show any increase in ARDS rates.
Acute kidney injury	Two studies reported the incidence of AKI. One study found no statistical difference in AKI between those receiving WB and those receiving component therapy. One study reported a higher incidence of AKI in the group receiving WB transfusion compared with		There was a significantly higher rate of AKI in the FWB group reported by Spinella et al. however, this difference was not replicated in the studies by Seheult et al. and Cotton et al.

	component therapy (8% vs 3% respectively, p=0.04).		
Multiple organ dysfunction syndrome	Two studies reported rates of MODS. Neither study found a statistically significant difference in MODS between those receiving WB transfusion and those receiving component therapy.		
Embolic events	Two studies reported rates of embolic events. Neither study found a statistically significant difference in embolic events between those receiving WB transfusion and those receiving component therapy.		

Cotton 2013 – randomized controlled trial
With respect to complications between mWB and COMP subjects, there were no differences in ventilator-dependent respiratory failure (29% vs 33%, P = 0.68), adult respiratory distress syndrome (0.0% vs 1.9%, P = 0.32), infectious complications (20% vs 17%, P = 0.72), severe sepsis/septic shock (4.5% vs 2.0%, P = 0.35), acute kidney injury/acute renal failure (2.0% vs 1.5%, P = 0.53), multiple organ failure (7.6% vs 9.0%, P = 0.79), or abdominal compartment syndrome (1.8% vs 1.9%, P = 0.97). There were no cases of transfusion-related acute lung injury in either group.

17. Acute transfusion reaction

Tre revisioni sistematiche riportano l'outcome di interesse. Di seguito si riporta una tabella riassuntiva dei risultati.

Outcome	**Avery 2020** (Qualitative synthesis)	**Cruciani 2020** (Quantitative synthesis but qualitative for the outcome of interest)	**Malkin 2020** (Qualitative synthesis)
Acute transfusion reaction	Three studies reported one transfusion reactions. Two studies reported no transfusion reactions in patients receiving WB transfusion. One study reported specifically no cases of transfusion-related acute lung injury in either group	Two transfusion reactions recorded in COMP recipients, none in LOTWB recipients. Not specified type of reaction in the systematic review.	None of the studies reported any transfusion related reactions in the WB or the component therapy groups

Cotton 2013 – randomized controlled trial
With respect to complications between mWB and COMP subjects, there were no differences in ventilator-dependent respiratory failure (29% vs 33%, P = 0.68), adult respiratory distress syndrome (0.0% vs 1.9%, P = 0.32), infectious complications (20% vs 17%, P = 0.72), severe sepsis/septic shock (4.5% vs 2.0%, P = 0.35), acute kidney injury/acute renal failure (2.0% vs 1.5%, P = 0.53), multiple organ failure (7.6% vs 9.0%, P = 0.79), or abdominal compartment syndrome (1.8% vs 1.9%, P = 0.97). There were no cases of transfusion-related acute lung injury in either group.

IMPORTANT OUTCOMES

18. Time to definitive control of haemorrhage

Subgroup children

Tra le prove disponibili, uno studio osservazionale-propensity-matched cohort (Leeper 2020) condotto sui bambini affetti da trauma maggiore riporta l'outcome di interesse.
Lo studio valuta l'efficacia in termini di "funciontal disability" misurata con in 28 bambini sottoposti a Low Titer Group O Whole Blood Transfusion Protocol e 28 bambini a component therapy.

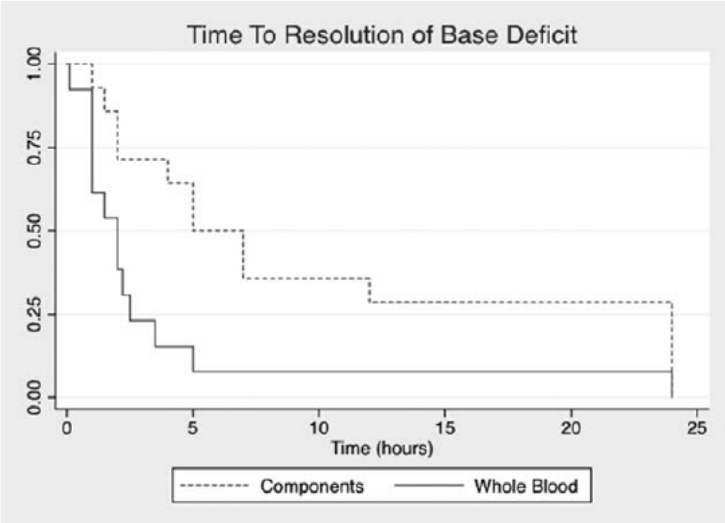


FIGURE 2. Time to resolution of base deficit was decreased in recipients of whole blood as compared to recipients of component products.

The whole blood group had faster time to resolution of base deficit [median (IQR) 2 (1–2.5) hours vs 6 (2–24) hours, respectively; P < 0.001].

19. Patient-reported outcomes: pain/discomfort return to normal activities psychological wellbeing)

Tra le prove di evidenza incluse, nessuna riporta l'outcome di interesse.

Appendice D – Valutazione della qualità metodologica degli studi inclusi

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

INDICE

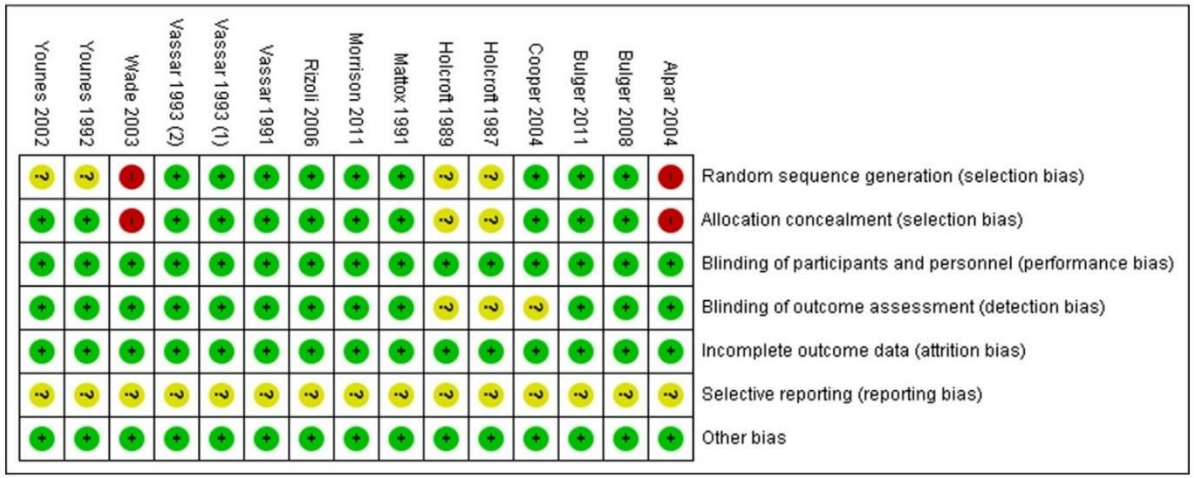
Comparison 1. Crystalloids vs crystalloids

Comparison 1: Hypertonic saline/dextran or hypertonic saline versus isotonic fluid (ie. normal saline/lactated Ringer's solution (LR))

Systematic review- Tabella 1. AMSTAR 2 - Methodological quality across systematic reviews

	Safiejko 2020
Total studies included in the RS; last date search update	15 RCTs, Search up to Agusut 20, 2020
Type of evidence synthesis	Quantitative and qualitative
overall quality	**CRITICALLY LOW**
1-Question and inclusion	yes
2-Protocol	no
3-Study design	no
4-Comprehensive search	yes
5-Study selection	yes
6-Data extraction	yes
7-Excluded studied justification	partial yes
8-Included studied details	yes
9-Risk of Bias	yes
10-Source of funding of included studies	no
11-Appropriate statistical methods for analysis	yes
12-Rob on meta-analyses	no
13-Rob on individual studies	yes
14-Explanation for heterogeneity	yes
15-Publication bias	no
16-Conflict of interest	yes

Risk of bias of RCT included In Safiejko 2020



Comparison 2: Normal saline versus lactated Ringer's solution (LR). Subgroup: TBI patients.

Observational study. Rowell 2016

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**tot**
	*	*	*	*	*	*	*	*	**8**
Rowell 2016		drawn from the same community as the exposed cohort	secure record	yes	To determine the effect of pre-hospital fluid type on mortality, a Cox proportional hazards model with random effects was created that included pre-hospital fluid type, pre-hospital fluid volume, ISS, AIS head, AIS extremity, age, pre-hospital intubation status, and study site.	record linkage: objective outcomes	yes		**Good quality**

Comparison 3: Plasma Lyte A versus normal saline

Randomized controlled trial – Young 2014.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	LOW RISK	computer-generated randomization sequence in a 1:1 ratio using a variable block size.
Allocation concealment (selection bias)	LOW RISK	They placed opaque wrappers around the IV fluid bags and labeled them with "Study Isotonic Crystalloid Fluid," a lot number, and an expiration date…We randomly allocated eligible subjects by breaking the seal on the next of the sequentially numbered suitcases
Blinding of participants and personnel (performance bias)	LOW RISK	The treating physicians, who were also blinded to the type of fluid being administered, determined the amount, frequency, and indications for fluid administration. Of note, although the treating physicians had access to laboratory data, blinding throughout the study was maintained
Blinding of outcome assessment (detection bias)	UNCLEAR RISK	The treating physicians, who were also blinded to the type of fluid being administered, determined the amount, frequency, and indications for fluid administration
Incomplete outcome data (attrition bias)	LOW RISK	Intention to treat analyses presented.
Selective reporting (reporting bias)	LOW RISK	"No changes to the trial protocol or outcomes occurred after we commenced the study." protocol registered on clinicaltrial.gov
Other bias	LOW RISK	Funding. This was an investigator-initiated trial supported by Baxter Healthcare (Deerfield, IL). Similarity at baseline. Subjects in the 2 treatment arms were similar in their baseline characteristics and injury severity

Comparison 2. Blood components vs standard care

Standard care= infusion with crystalloids, no transfusion, unknown or combination with blood components

Tabella 1. AMSTAR 2 – Methodological quality across systematic reviews **Errore. Il collegamento non è valido.**

	Rijnhout 2019	**Coccolini 2019**
	2RCT and	2 RCT
OVERALL QUALITY	**critically Low**	**critically Low**
1-Question and inclusion	no	no
2-Protocol	no	no
3-Study design	no	yes
4-Comprehensive search	partially yes	partially yes
5-Study selection	yes	yes
6-Data extraction	no	yes
7-Excluded studied justification	no	no
8-Included studied details	yes	no
9-Risk of Bias	yes	yes
10-Source of funding of included studies	no	no
11-Appropriate statistical methods for analysis	yes	yes
12-Rob on meta-analyses	yes	partially yes
13-Rob on individual studies	yes	yes
14-Explanation for heterogeneity	yes	yes
15-Publication bias	NA	partially yes
16-Conflict of interest	yes	yes

Rijnhout 2019 risk of bias of included studies:

APPENDIX S7 Risk of Bias for studies included in meta-analysis (ROBINS-I)

Study (Reference)	Confounding	Selection	Classification of interventions	Deviation from intervention	Missing data	Measurements of outcomes	Reported result	Overall
Rehn *et al.* (4)	SR	SR	LR	LR	CR	LR	LR	CR
Peters *et al.* (51)	SR	SR	LR	NI	CR	LR	LR	CR
Shackelford *et al.* (52)	SR	LR	LR	LR	MR	LR	LR	SR
Holcomb *et al.* (53)	CR	CR	LR	LR	LR	LR	LR	CR
Miller *et al.* (49)	CR	CR	LR	LR	LR	LR	LR	CR
Brown II *et al.* (6)	CR	CR	LR	LR	LR	LR	LR	CR
O'reilly II *et al.* (61)	MR	CR	LR	LR	MR	LR	LR	CR

Legend: LR = low risk; MR=moderate risk; SR=serious risk CR=critical risk; NI = no information

APPENDIX S8 Risk of Bias for studies included in meta-analysis (Cochrane) Moore 2018 and Sperry 2018

Study (Reference)	Selection bias: random sequence allocation	Selection bias: allocation concealment	Performance bias: Blinding of participants and personnel	Detection bias: blinding of outcome assessment	Attrition bias: incomplete outcome data	Reporting bias: selective reporting	Other sources of bias	Overall
Sperry *et al.* (64)	LR	LR	HR	LR	LR	HR	LR	HR
Moore *et al.* (65)	UR	LR	HR	LR for primary outcomes UR for secondary outcomes	LR	UR	LR	HR

Legend: LR = low risk; HR= high risk; UR = unknown risk

Both studies were at high risk of performance bias, because (full) blinding of personnel and patients could not be performed. One study appeared to be at risk of reporting bias, since data for two secondary outcomes mentioned in the study protocol were not reported.

Overall, for this 2 secondary outcomes we go through the reading of primary studies for the SOF assessment. Overall judgement :LOW RISK

Coccolini 2019 risk of bias of included studies (Moore 2018 and Sperry 2018):

Table 1 Study quality

Study (ref.), year	Randomisation	Allocation concealment	Homogeneous baseline characteristic	Eligibility criteria	Loss to follow-up and drop-out described	Intention-to-treat analysis	Study quality
Moore [9], 2018	Yes	Yes	Yes	Yes	Yes	Yes	High
Sperry [10], 2018	Yes	Yes	Yes	Yes	Yes	Yes	High

Tabella 2. Studi osservazionali:

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**tot**
Griggs 2018 retrospective observational cohort	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (Risk adjustment was performed by creating a multivariate logistic regression model to predict both mortalities, utilising the covariates age, SBP, ISS, MOI.)	* record linkage: objective outcomes	* yes	Subjects lost to follow up likely to introduce biasδ	**7 Good quality**
Ditillo 2020 retrospective cohort analysis of the American College of Surgeons	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (We adjusted for patient demographics, insurance status, vital parameters, injury-related parameters, patient comorbidities, ACS verification level, and hemorrhage control interventions. The performance of all multivariable logistic regression models)	* record linkage: objective outcomes	* yes	* No information	**8 Good quality**

δLoss to follow up, and incomplete patient records from oth the pre-hospital and in-hospital phases, produced substantial missing data. Notably, 26% of follow up data is missing in the crystalloid group. To address this, Multiple imputations of 10 datasets was employed

Comparison 3. Blood components ratio

3.1- FFP:PLT:PRBC ratio

Tabella 1. AMSTAR 2 – Methodological quality across systematic reviews

	McQuilten 2018 6 trials; search up to 21st February 2017	**Luz 2019** 55 (2 trial and 53 observational), search up to July 31, 2018	**Ritchie 2020** 7 RCTs, Search 7up to May 10, 2019
OVERALL QUALITY	**Moderate**	**Low**	**Low**
1-Question and inclusion	yes	yes	yes
2-Protocol	yes	no	no
3-Study design	no	no	no
4-Comprehensive search	yes	yes	partial yes
5-Study selection	yes	yes	no
6-Data extraction	yes	yes	no
7-Excluded studied justification	partial yes	partial yes	partial yes
8-Included studied details	yes	yes	yes
9-Risk of Bias	yes	yes	yes
10-Source of funding of included studies	no	no	no
11-Appropriate statistical methods for analysis	yes	yes	not applicable
12-Rob on meta-analyses	yes	yes	not applicable
13-Rob on individual studies	yes	yes	yes
14-Explanation for heterogeneity	yes	yes	yes
15-Publication bias	yes	yes	not applicable
16-Conflict of interest	yes	yes	yes

3.2 - FFP:PRBC ratio

Tabella 2. AMSTAR 2 – Methodological quality across systematic reviews

	Luz 2019 55 (2 trial and 53 observational), search up to July 31, 2018	**Rodríguez 2020** 33 studies (2 clinical trials and 31 observational studies); search between the first week of 1990 and week 40 of 2019	**Poole 2016** 9 observational studies; search date December 14 2014	**Rahouma 2018** 36 stidies (2 trials, 24 observational); search up to January 10th, 2016	**Writz 2020** 39 (6 trial and 33 observational), search up to
OVERALL QUALITY	**LOW**	**MODERATE**	**VERY LOW**	**VERY LOW**	**VERY LOW**
1-Question and inclusion	yes	yes	yes	yes	yes
2-Protocol	no	yes	no	no	no
3-Study design	no	no	no	no	no
4-Comprehensive search	yes	yes	no	yes	yes
5-Study selection	yes	yes	yes	yes	yes
6-Data extraction	yes	yes	yes	yes	yes
7-Excluded studied justification	partial yes	partial yes	partial yes	partial yes	no
8-Included studied details	yes	yes	yes	yes	yes
9-Risk of Bias	yes	yes	yes	yes	yes
10-Source of funding of included studies	no	no	no	no	no
11-Appropriate statistical methods for analysis	yes	yes	NA	no	no
12-Rob on meta-analyses	yes	yes	NA	yes	yes
13-Rob on individual studies	yes	yes	yes	yes	yes
14-Explanation for heterogeneity	yes	yes	no	yes	yes
15-Publication bias	yes	yes	NA	yes	no
16-Conflict of interest	yes	yes	no	yes	no

Tabella 3. Studi osservazionali

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**tot**
Cannon 2017	*	*	*	*	**	*	*	*	**9**
Haltmeier 2018		*	*	*	**	*	*	*	**8**
Sehdev 2020	*	*	*	*	*	*	*	*	**8**
Nederpelt 2019	*	*	*	*	**	*	*		**8**
Cunningham 2019	*	*	*	*		*	*	*	**7**
Butler 2019	*	*	*	*	**	*	*	*	**9**

3.3 - PLT:PRBC ratio

Tabella 4. AMSTAR 2 – Methodological quality across systematic reviews

	Luz 2019 55 (2 trial and 53 observational), search up to July 31, 2018	**Writz 2020** 39 (6 trial and 33 observational), search up to
OVERALL QUALITY	**LOW**	**VERY LOW**
1-Question and inclusion	yes	yes
2-Protocol	no	no
3-Study design	no	no
4-Comprehensive search	yes	yes
5-Study selection	yes	yes
6-Data extraction	yes	yes
7-Excluded studied justification	partial yes	no
8-Included studied details	yes	yes
9-Risk of Bias	yes	yes
10-Source of funding of included studies	no	no
11-Appropriate statistical methods for analysis	yes	no
12-Rob on meta-analyses	yes	yes
13-Rob on individual studies	yes	yes
14-Explanation for heterogeneity	yes	yes
15-Publication bias	yes	no
16-Conflict of interest	yes	no

Tabella 5. Studi osservazionali

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**tot**
Cunningham 2019	*	*	*	*		*	*	*	**7 Good quality**
Butler 2019	*	*	*	*	**	*	*	*	**9 Good quality**

Comparison 4. Whole blood vs component therapy (blood components)

Component therapy= standard component therapy (red blood cells, plasma, and platelets)

Tabella 1. AMSTAR 2 - Methodological quality across systematic reviews.

	McQuilten 2018	**Crowe 2020**	**Avery 2020**	**Cruciani 2020**	**Malkin 2020**
	6 trials; search up to 21st February 2017	12 studies: retrospective cohort (n = 10), prospective cohort (n = 1), and randomized control trial (n =1); search from January 2007 to June 2019.	Six studies: 1 prospective randomised trial, 1 prospective with historical controls, 4 retrospective analyses. from the inception of the databases to the search date (15th December 2019).	7 studies: 1 RCT, 6 observational. latest search March 6, 2020	5 studies: 1 RCT, 4 OBS retrospective; search up to 2018
	Whole Blood VS Component therapy	Whole Blood VS Component therapy	Whole Blood VS Component therapy	Whole Blood VS Component therapy	Whole Blood VS Component therapy
	Quantitative and qualitative	Quantitative and qualitative	Only qualitative	Quantitative and qualitative	Only qualitative
OVERALL QUALITY	**MODERATE**	**CRITICALLY LOW**	**LOW**	**CRITICALLY LOW**	**MODERATE**
1-Question and inclusion	yes	yes	yes	yes	yes
2-Protocol	yes	yes	yes	no	yes
3-Study design	no	no	no	no	no
4-Comprehensive search	yes	partial yes	yes	partial yes	partial yes
5-Study selection	yes	yes	yes	yes	yes
6-Data extraction	yes	yes	yes	yes	yes
7-Excluded studied justification	partial yes	partial yes	no	no	partial yes
8-Included studied details	yes	yes	yes	yes	no
9-Risk of Bias	yes	yes	yes	yes	yes
10-Source of funding of included studies	no	no	no	no	no
11-Appropriate statistical methods for analysis	yes	no	not applicable	no	not applicable
12-Rob on meta-analyses	yes	no	not applicable	yes	not applicable
13-Rob on individual studies	yes	no	yes	yes	yes
14-Explanation for heterogeneity	yes	yes	yes	yes	yes
15-Publication bias	yes	yes	yes	yes	yes
16-Conflict of interest	yes	yes	yes	no	no

Randomized controlled trial – Cotton 2013

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	UNCLEAR	Randomized the patient by opening a sealed envelope with the assigned study group (WB or COMP).
Allocation concealment (selection bias)	LOW RISK	Randomized the patient by opening a sealed envelope with the assigned study group (WB or COMP).
Blinding of participants and personnel (performance bias)	HIGH RISK	Once the seal of the cooler was broken, the patient was considered enrolled in the study (per-protocol group) and study and clinical personnel were then unblinded to treatment group.
Blinding of outcome assessment (detection bias)	HIGH RISK	Once the seal of the cooler was broken, the patient was considered enrolled in the study (per-protocol group) and study and clinical personnel were then unblinded to treatment group
Incomplete outcome data (attrition bias)	LOW RISK	Per protocol and intention to treat analysis
Selective reporting (reporting bias)	UNCLEAR RISK	No published protocol
Other bias	LOW RISK	Funding. Supported by a grant from the Department of Defense via W81XWH-08-C-0712. Similarity at baseline. As with the intent-to-treat group, there were no differences in demographics or baseline data

Observational study - Leeper 2020

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**tot**
	*	*	*	*	*	*	*	*	**Good quality**
Leeper 2020 retrospective observational cohort		drawn from the same community as the exposed cohort	secure record	yes	Propensity-score matching was used to identify a cohort of patients with similar baseline characteristics that were known contributors to trauma-induced coagulopathy, transfusion requirement and poor outcome in pediatric trauma patients.	record linkage: objective outcomes	yes		

Criteria for judgements of quality assessment tools

AMSTAR

High - Zero or one non-critical weakness: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Moderate - More than one non-critical weakness*: The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

Low - One critical flaw with or without non-critical weaknesses: The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Critically low - More than one critical flaw with or without non-critical weaknesses: The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

*Note: Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

RISK OF BIAS – COCHRANE TOOL

Domain	**Support for judgement**	**Review authors' judgement**
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes)*.	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		

Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

NEW CASTLE OTTAWA SCALE

To assess the quality of nonrandomised studies with its design, content and ease of use we used the New castle Ottawa Scale. A 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.

GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Appendici E1-E4 – Tabelle delle evidenze

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

Appendice E1 – Tabelle delle evidenze. Comparazione: crystalloids vs crystalloids

Criteri for Downgrade

risk of bias:
-1 high or unclear risk of selection (randomizzazione e allocazione) or outcome reporting bias
-2 high or unclear risk of selection (randomizzazione e allocazione) and outcome reporting bias

imprecision:
-1 events<200 or < 400 patients or confidence intervals crossed the line of no difference with plausible effects in favor to the experimental/group group or wide confidence intervals
-2 al least two of the above conditions

indirectness:
-1 for setting (e.g., in-hospital)
-2 for setting (e.g., in-hospital) and not enough information for PICO description (e.g., trauma and no-truama)

inconsistency:
-1 for statistical inconsistecy I^2 >75% or methodological inconsistency (e.g., RCT and observational studies pooled together)
-2 for statistical inconsistecy I^2 >90%

publication bias:
-1 If n studies>10 and the Sr did not investigate the publication bias
-2 If high risk of publication bias

In case of observational studies, we upgrade for the following domains:
Large magnitude of effect: This is a result of a study or meta-analysis and should not be used as a quality criterion. Large magnitude of effect may imply a high risk of biased results rather than increased confidence in results

Dose-response gradient: often exists in studies assessing etiology of disease, but effectiveness of an intervention usually does not show a linear dose-response pattern

Residual confounding: would further support inferences regarding treatment effect If some plausible confounders have not been documented, there is no credible way to determine how adjusting these parameters would alter the effectiveness estimates.

Appendice E1. Summary of Findings: crystalloids vs crystalloids

			Safiejko 2020	Rowell 2016	Young 2014
		Comparisons	**Hypertonic saline/dextran or hypertonic saline versus isotonic fluid**	**Normal saline versus lactated Ringer's solution**	**Plasma Lyte A versus normali saline**
		Study design	Systematic Review of RCTs	Observational study	Randomized controlled trial
	1a	**24 h mortality**	***24 h survival*** Survival to hospital discharge rate 88.6% in hypertonic saline/dextran (HSD) group vs. 72.3% for isotonic fluid (NS) solutions (OR = 2.99; 95% CI 2.04–4.39; I2 = 0%; p = 0.09; 9 trials).	not assessed	not assessed
		risk of bias	Not serious		
		imprecision	Not serious		
		indirectness	Not serious		
		inconsistency	Not serious		
		publication bias	None		
		Other considerations			
		QUALITY of EVIDENCE	**HIGH**		
	1b	**Mortality at discharge**	Survival to hospital discharge rate 71.2% in hypertonic saline/dextran (HSD) group vs. 68.4% for isotonic fluid (NS) solutions (OR = 1.19; 95% CI 0.97–1.45; I2 = 48%; p = 0.09). Subgroup: - hypertonic saline/dextran (HSD) vs isotonic fluid (NS) solutions: OR 1.13 (95% CI 0.89 – 1.44, I2=36%, p=0.14)	not assessed	not assessed

			Safiejko 2020	Rowell 2016	Young 2014
		Comparisons	**Hypertonic saline/dextran or hypertonic saline versus isotonic fluid**	**Normal saline versus lactated Ringer's solution**	**Plasma Lyte A versus normali saline**
		Study design	Systematic Review of RCTs	Observational study	Randomized controlled trial
			- hypertonic saline vs isotonic fluid (NS) solutions: OR 1.10 (95% CI 0.83 – 1.44, I2=0%, p=0.56)		
		risk of bias	Not serious		
		imprecision	Serious		
		indirectness	Not serious		
		inconsistency	Not serious		
		publication bias	None		
		Other considerations			
		QUALITY of EVIDENCE	**MODERATE**		
critical	1c	**Mortality at 30 days**	Survival 28 – 30 days Pooled analysis showed that the use of hypertonic fluid solutions was 72.8% survivable, while in the case of isotonic fluid (NS) 71.4% (OR = 1.13; 95% CI 0.75–1.70; I2 = 43%; p = 0.56; 5 trials).	Increased mortality in the LR group compared with the NS group at 30 days (HR 1.78, CI 1.04–3.04, p = 0.035).	In-hospital mortality at 30 days 0R 0.8, CI 0.2 – 3.3
		risk of bias	Not serious	Not serious	Not serious
		imprecision	Serious	Serious	Very serious
		indirectness	Not serious	Not serious	Not serious
		inconsistency	Not serious	Not serious	Not serious
		publication bias	None	none	None
		Other consideration		Large effect	
		QUALITY of EVIDENCE	**MODERATE**	**LOW**	**LOW**
	1d	**Overall mortality**	Overall mortality Pooled analysis showed that the use of hypertonic fluid solutions was 19.7%, while 24.8% in the case of isotonic fluid (NS) — 71.4% (OR 0.76 (95% IC 0.61 – 0.94; i2=33%; 7 trials).	not assessed	not assessed

			Safiejko 2020	Rowell 2016	Young 2014
		Comparisons	**Hypertonic saline/dextran or hypertonic saline versus isotonic fluid**	**Normal saline versus lactated Ringer's solution**	**Plasma Lyte A versus normali saline**
		Study design	Systematic Review of RCTs	Observational study	Randomized controlled trial
		risk of bias	Not serious		
		imprecision	Serious		
		indirectness	Not serious		
		inconsistency	Not serious		
		publication bias	None		
		Other considerationsa			
		QUALITY of EVIDENCE	**MODERATE**		
	2	**Health related-quality of life**	not assessed	not assessed	not assessed
		risk of bias			
		imprecision			
		indirectness			
		inconsistency			
		publication bias			
		Other considerations			
		QUALITY of EVIDENCE			
	3	**Lenght of intensive care stay**	The use of hypertonic fluid was associated with a longer hospital stay than with isotonic fluid solutions (mean difference [MD] = 1.45; 95% CI 0.43–2.46; p = 0.005).	not assessed	0.9% NaCl (n = 24) days median IQR: 4 (2, 13); Plasma-Lyte (n = 22) days median IQR: 4 (1, 9)
		risk of bias	Not serious		Not serious
		imprecision	Serious		Not judgment possible
		indirectness	Not serious		Not serious

			Safiejko 2020	Rowell 2016	Young 2014
		Comparisons	**Hypertonic saline/dextran or hypertonic saline versus isotonic fluid**	**Normal saline versus lactated Ringer's solution**	**Plasma Lyte A versus normali saline**
		Study design	Systematic Review of RCTs	Observational study	Randomized controlled trial
		inconsistency	Not serious		Not serious
		publication bias	None		None
		Other considerations			
		QUALITY of EVIDENCE	**MODERATE**		-
	4	**Adverse effects**		not assessed	There were no identifiable adverse events in either arm.
		risk of bias			Not serious
		imprecision			Not judgment possible
		indirectness			Not serious
		inconsistency			Not serious
		publication bias			None
		Other considerations			
		QUALITY of EVIDENCE			-
	5	**Acute transfusion reaction**		not assessed	not assessed
		risk of bias			
		imprecision			
		indirectness			
		inconsistency			
		publication bias			
		Other considerations			
		QUALITY of EVIDENCE			
	2	**Time to definitive control of haemorrhage**	not assessed	not assessed	not assessed

			Safiejko 2020	Rowell 2016	Young 2014
		Comparisons	**Hypertonic saline/dextran or hypertonic saline versus isotonic fluid**	**Normal saline versus lactated Ringer's solution**	**Plasma Lyte A versus normali saline**
		Study design	Systematic Review of RCTs	Observational study	Randomized controlled trial
		risk of bias			
		imprecision			
		indirectness			
		inconsistency			
		publication bias			
		Other considerations			
		QUALITY of EVIDENCE			
	3	**Patient-reported outcomes**	not assessed	not assessed	not assessed
		risk of bias			
		imprecision			
		indirectness			
		inconsistency			
		publication bias			
		Other considerations			
		QUALITY of EVIDENCE			

Appendice E2 – Tabelle delle evidenze. Comparazione 2: blood products versus standard care

INDICE

Criteri di Giudizio

Criteri per Downgrade

risk of bias:
-1 high or unclear risk of selection (randomizzazione e allocazione) or outcome reporting bias
-2 high or unclear risk of selection (randomizzazione e allocazione) and outcome reporting bias

imprecision:
-1 events<200 or < 400 patients or confidence intervals crossed the line of no difference with plausible effects in favor to the experimental/group group or wide confidence intervals
-2 al least two of the above conditions

indirectness:
-1 for setting (e.g., in-hospital)
-2 for setting (e.g., in-hospital) and not enough information for PICO description (e.g., trauma and no-truama)

inconsistency:
-1 for statistical inconsistecy I^2 >75% or methodological inconsistency (e.g., RCT and observational studies pooled together)
-2 for statistical inconsistecy I^2 >90%

publication bias:
-1 If n studies>10 and the Sr did not investigate the publication bias

Criteri per Upgrade (in addition for observational studies)

Large magnitude of effect: This is a result of a study or meta-analysis and should not be used as a quality criterion. Large magnitude of effect may imply a high risk of biased results rather than increased confidence in results

Dose-response gradient: often exists in studies assessing etiology of disease, but effectiveness of an intervention usually does not show a linear dose-response pattern

Residual confounding: would further support inferences regarding treatment effect If some plausible confounders have not been documented, there is no credible way to determine how adjusting these parameters would alter the effectiveness estimates.

Appendice E2.1. Summary of Findings: packed red blood cells (PRBCs) versus standard care

		SR: Rijnhout 2019	primary study: Griggs 2018
1a	**Mortality at 24 hours**	3 retrospective studies OR = 0.92; 95% CI, 0.46–1.85; P = 0.82	1 observational studies, adjusted odds ratios (OR), after multiple imputation for both 6 h and 28 d mortality show no statistically significant association
	risk of bias	serious	not serious
	imprecision	not serious	serious
	indirectness	not serious	serious
	inconsistency	serious	not serious
	publication bias	none	none
	Other consideration	none	none
	QUALITY of EVIDENCE	**VERY LOW**	**VERY LOW**
1b	**Mortality at long term (30 days/1month and 12 months)**	4 retrospective studies OR = 1.18; 95% CI, 0.93–1.49; P = 0.17	1 observational studies, adjusted odds ratios (OR), after multiple imputation for both 6 h and 28 d mortality show no statistically significant association
	risk of bias	serious	not serious
	imprecision	not serious	serious
	indirectness	not serious	serious
	inconsistency	not serious	not serious
	publication bias	none	none
	Other consideration	none	none
	QUALITY of EVIDENCE	**VERY LOW**	**VERY LOW**
2	**Health related-quality of life**	not assessed	not assessed
	QUALITY of EVIDENCE		
3	**Length of intensive care stay**	not assessed	not assessed
	QUALITY of EVIDENCE		
4	**Adverse effects**	In a total of 1341 patients who received PHBT, 14 adverse events were reported 1.04%, 95% CI 0.57–1.75%. However, not all included studies reported adverse events, which means that this number may be an underestimation of the actual number.	not assessed
	QUALITY of EVIDENCE		
5	**Acute transfusion reaction**	14 studies. Complication which was possibly related to the transfusion (1.04%, 95% CI 0.57–1.75%)	During the study period there were no immediate transfusion complications, and 100% traceability of pre-hospital PRBC was achieved.
	risk of bias	serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	Other consideration	none	

	QUALITY of EVIDENCE	**VERY LOW**	
1	**Time to definitive control of haemorrhage**	not assessed	not assessed
	QUALITY of EVIDENCE		
2	**Patient-reported outcomes: return to normal activities psychological wellbeing)**	not assessed	not assessed
	QUALITY of EVIDENCE		

Appendice E2.2. Summary of Findings: packed red blood cells (PRBCs) + plasma versus standard care

	SR	Rijnhout 2019 (SR up to august 2018)		Coccolini 2019 (SR up to august 2018)
1a	**Mortality at 24 hours**		2 retrospective studies in Rijnhout 2019 (SR up to august 2018) OR = 0.47, 95% CI, 0.17–1.34; P = 0.16	
	risk of bias		not serious	
	imprecision		serious	
	indirectness		not serious	
	inconsistency		not serious	
	publication bias		not serious	
	Other consideration		none	
	QUALITY of EVIDENCE		**VERY LOW**	
1b	**Mortality at long term (30 days/1month and 12 months)**	1 trials in Rijnhout 2019 (SR up to august 2018) OR = 0.51; 95% CI, 0.33–0.81; P < 0.0001	3 retrospective studies in Rijnhout 2019 (SR up to august 2018) OR = 0.49; 95% CI, 0.23–0.83 P < 0.008	
	risk of bias	not serious	not serious	
	imprecision	serious	not serious	
	indirectness	not serious	not serious	
	inconsistency	not serious	not serious	
	publication bias	not serious	not serious	
	Other consideration		none	
	QUALITY of EVIDENCE	**MODERATE**	**LOW**	
2	**Health related-quality of life**	not assessed		not assessed
	QUALITY of EVIDENCE			
3	**Length of intensive care stay**	1 trial: Moore 2018 Intensive-care-free day in plasma group: 23 (7 to 26), standard care: 24 (17 to 26), 0 (−3·00 to 1·00) p=0·49		
	risk of bias	not serious		
	imprecision	serious		
	indirectness	not serious		
	inconsistency	not serious		
	publication bias	not serious		
	QUALITY of EVIDENCE	**MODERATE**		
4	**Adverse effects**	In a total of 1341 patients who received PHBT, 14 adverse events were reported 1.04%, 95% CI 0.57–1.75%. However, not all included studies reported adverse events, which means that this number may be an underestimation of the actual number.		not assessed
		1 trial: Sperry 2018: N°of patients with AEs: 2 in the standard care group (n=271) and 6 in the plasma group (n=230);		

		N°of AEs: 4 in the standard care group (n=271) and 6 in the plasma group (n=230)	
	risk of bias	not serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	QUALITY of EVIDENCE	**MODERATE**	
5	**Acute transfusion reaction**	1 trial: Sperry 2018: 2 allergic reaction in the standard care group (n=271) and 0 in the plasma group (n=230)	
	risk of bias	not serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	QUALITY of EVIDENCE	**MODERATE**	
		14 studies. Complication which was possibly related to the transfusion (1.04%, 95% CI 0.57–1.75%)	
	risk of bias	serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	Other consideration	none	
	QUALITY of EVIDENCE	**VERY LOW**	
1	**Time to definitive control of haemorrhage**	not assessed	not assessed
	QUALITY of EVIDENCE		
2	**Patient-reported outcomes: return to normal activities psychological wellbeing)**	not assessed	not assessed
	QUALITY of EVIDENCE		

Appendice E2.3. Summary of Findings: Plasma versus standard care.

	SR	**Rijnhout 2019**	**Coccolini 2019**
1a	Mortality at 24 hours	1 trial: Moore 2018 More patients in the plasma group died than in the control group, but not significantly (p=0.68)	2 trials, (RR = 0.69; 95% CI = 0.48–0.99)
	risk of bias	not serious	not serious
	imprecision	serious	not serious
	indirectness	not serious	not serious
	inconsistency	not serious	not serious
	publication bias	not serious	none
	QUALITY of EVIDENCE	**MODERATE**	**HIGH**
1b	Mortality at 30 days/1month	1 trial: Moore 2018 More patients in the plasma group died than in the control group, but not significantly (p=0.37)	2 trials, (RR = 0.86; 95% CI = 0.68–1.11)
	risk of bias	not serious	not serious
	imprecision	serious	serious
	indirectness	not serious	not serious
	inconsistency	not serious	not serious
	publication bias	not serious	not serious
	QUALITY of EVIDENCE	**MODERATE**	**MODERATE**
2	**Health related-quality of life**	not assessed	not assessed
	QUALITY of EVIDENCE		
3	**Length of intensive care stay**	1 trial: Moore 2018 Intensive-care-free day in plasma group: 23 (7 to 26), standard care: 24 (17 to 26), 0 (−3·00 to 1·00) p=0·49	
	risk of bias	not serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	QUALITY of EVIDENCE	**MODERATE**	
4	**Adverse effects**	1 trial: Sperry 2018 N°of patients with AEs: 2 in the standard care group (n=271) and 6 in the plasma group (n=230); N°of AEs: 4 in the standard care group (n=271) and 6 in the plasma group (n=230)	
	risk of bias	not serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	QUALITY of EVIDENCE	**MODERATE**	
5	**Acute transfusion reaction**	1 trial Sperry 2018:	

		One transfusion- related or allergic reaction (0.4%) was reported in the standard-care group.	
	risk of bias	not serious	
	imprecision	serious	
	indirectness	not serious	
	inconsistency	not serious	
	publication bias	not serious	
	QUALITY of EVIDENCE	**MODERATE**	
1	**Time to definitive control of haemorrhage**	not assessed	not assessed
	QUALITY of EVIDENCE		
2	**Patient-reported outcomes: return to normal activities psychological wellbeing)**	not assessed	not assessed
	QUALITY of EVIDENCE		

Appendice E2.4. Summary of Findings: Packed red blood cells (PRBCs) + cryoprecipitate verus no cryoprecipitate

	Observational study	**Ditillo 2018**
1a	**Mortality at 24 hours**	OR, 0.78 [0.63–0.84], p = 0.02)
	risk of bias	not serious
	imprecision	serious
	indirectness	not serious
	inconsistency	not serious
	publication bias	none
	Other consideration	none
	QUALITY of EVIDENCE	**VERY LOW**
1b	**Mortality in-hospital**	in-hospital mortality (OR, 0.79 [0.77–0.87], p = 0.01)
	risk of bias	not serious
	imprecision	serious
	indirectness	not serious
	inconsistency	not serious
	publication bias	none
	Other consideration	none
	QUALITY of EVIDENCE	**VERY LOW**
2	**Health related-quality of life**	not assessed
	QUALITY of EVIDENCE	
3	**Length of intensive care stay**	not assessed
	QUALITY of EVIDENCE	
4	**Adverse effects**	in-hospital complications (OR, 1.48 [0.71–1.99], p = 0.31)
	risk of bias	not serious
	imprecision	serious
	indirectness	not serious
	inconsistency	not serious
	publication bias	none
	Other consideration	none
	QUALITY of EVIDENCE	**VERY LOW**
5	**Acute transfusion reaction**	not assessed
	QUALITY of EVIDENCE	
1	**Time to definitive control of haemorrhage**	not assessed
	QUALITY of EVIDENCE	
2	**Patient-reported outcomes: return to normal activities psychological wellbeing)**	not assessed
	QUALITY of EVIDENCE	

Appendice E2.5. Summary of Findings: High C:PRBC vs Low C:PRBC

Adopted from NICE NG39: multicenter prospective cohort study (Neal 2012)

Table 79: Clinical evidence summary: Crystalloid: RBCs

Outcome	Number of studies (no. of participants)	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Relative High versus low	Control event rate for continuous outcomes
Mortality (in hospital)	1 (n=452)	Very serious	VERY LOW	GIV	No adjusted data presented	OR 0.9 (0.58 to 1.45)	-
Nosocomial infection	1 (n=452)	Very serious	VERY LOW	GIV	No adjusted data presented	OR 1.3 (0.68 to 2.5)	-
Multiple organ failure	1 (n=452)	Serious	VERY LOW	GIV	No adjusted data presented	OR 1.7 (1.2 to 2.6)	-
Acute respiratory distress syndrome	1 (n=452)	None	VERY LOW	GIV	No adjusted data presented	OR 2.2 (1.5 to 3.1)	-

Appendice E3 – Tabelle delle evidenze. Comparazione 2: blood products ratio

INDICE

Criteri di Giudizio

Criteri per Downgrade

risk of bias:
-1 high or unclear risk of selection (randomizzazione e allocazione) or outcome reporting bias
-2 high or unclear risk of selection (randomizzazione e allocazione) and outcome reporting bias

imprecision:
-1 events<200 or < 400 patients or confidence intervals crossed the line of no difference with plausible effects in favor to the experimental/group group or wide confidence intervals
-2 al least two of the above conditions

indirectness:
-1 for setting (e.g., in-hospital)
-2 for setting (e.g., in-hospital) and not enough information for PICO description (e.g., trauma and no-truama)

inconsistency:
-1 for statistical inconsistecy I^2 >75% or methodological inconsistency (e.g., RCT and observational studies pooled together)
-2 for statistical inconsistecy I^2 >90%

publication bias:
-1 If n studies>10 and the Sr did not investigate the publication bias

Criteri per Upgrade (in addition for observational studies)

Large magnitude of effect: This is a result of a study or meta-analysis and should not be used as a quality criterion. Large magnitude of effect may imply a high risk of biased results rather than increased confidence in results

Dose-response gradient: often exists in studies assessing etiology of disease, but effectiveness of an intervention usually does not show a linear dose-response pattern

Residual confounding: would further support inferences regarding treatment effect If some plausible confounders have not been documented, there is no credible way to determine how adjusting these parameters would alter the effectiveness estimates.

Appendice E3.1- Summary of Findings - FFP PLT PRBC

SR identification		SR characteristics	**McQuilten 2018 Transfusion Medicine Reviews** 6 trials; search up to 21st February 2017	**Luz 2019 Transfusion** 55 (2 trial and 53 observational), search up to July 31, 2018	**Ritchie 2020 Trauma Acute Care Surg** 7 RCTs, Search 7up to May 10, 2019
critical	1	**Mortality at 1 month**	2 RCTs, n=755; RR=1.26; 95% CI: 0.49-3.22, I2=75%	2 RCTs, n=755; OR 1.35; 95% CI: 0.40-4.59, I2=76%	2 RCTs, n=755;
		risk of bias	serious	not serious	
		imprecision	serious	serious	
		indirectness	not serious	not serious	
		inconsistency	serious	serious	
		publication bias	none	none	
		QUALITY of EVIDENCE	**VERY LOW**	**LOW**	QUALITATIVE
	2	**Health related-quality of life**	not assessed	not assessed	not assessed
		risk of bias			
		imprecision			
		indirectness			
		inconsistency			
		publication bias			
		QUALITY of EVIDENCE			
	3	**Length of ICU stay**	2 RCTs, n=755;		2 RCTs, n=755;
		risk of bias			
		imprecision			
		indirectness			
		inconsistency			
		publication bias			
		QUALITY of	ONLY DESCRIPTIVE		ONLY DESCRIPTIVE

SR identification		SR	**McQuilten 2018 Transfusion Medicine Reviews**	**Luz 2019 Transfusion**	**Ritchie 2020 Trauma Acute Care Surg**
		characteristics	6 trials; search up to 21st February 2017	55 (2 trial and 53 observational), search up to July 31, 2018	7 RCTs, Search 7up to May 10, 2019
		EVIDENCE			
critical	4	**Adverse effect** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	1 RCT, n=680 ONLY DESCRIPTIVE	not assessed	1 RCT, n=680 ONLY DESCRIPTIVE
	5	**Acute transfusion reaction** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	1 RCT, n=680 ONLY DESCRIPTIVE	not assessed	not assessed
important	1	**Time to definitive control of haemorrhage** risk of bias imprecision indirectness	not assessed	not assessed	not assessed

		SR	McQuilten 2018 Transfusion Medicine Reviews	Luz 2019 Transfusion	Ritchie 2020 Trauma Acute Care Surg
SR identification		characteristics	6 trials; search up to 21st February 2017	55 (2 trial and 53 observational), search up to July 31, 2018	7 RCTs, Search 7up to May 10, 2019
		inconsistency publication bias **QUALITY of EVIDENCE**			
	2	**Patient-reported outcomes** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed	not assessed

Appendice E3.2. Summary of Findings - FFP PRBC ratio

SR identification		SR	Luz 2019	Rodríguez 2020	Poole 2016	Rahouma 2018	Writz 2020
		characteristics	55 (2 trial and 53 observational), search up to July 31, 2018	33 studies (2 clinical trials and 31 observational studies); search between the first week of 1990 and week 40 of 2019	9 observational studies; search date December 14 2014	36 stidies (2 trials, 24 observational); search up to January 10th, 2016	39 (6 trial and 33 observational), search up to
critical	1	**Mortality** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of**	**FFP:RBC 1:1 vs <1:1** (24 hours: 5 observational studies, OR=0.34; 95% CI = 0.14-0.82; 30 days: 10 observational studies, OR=0.38; 95% CI = 0.22-0.68) **FFP:RBC 1:1.5 vs <1:1.5** (24 hours: 2 observational studies, OR=0.43; 95% CI = 0.18-1.06; 30 days: 5 observational studies, OR=0.42; 95% CI = 0.22-0.81) **FFP:RBC 1:2 vs <1:2** (24 hours: 6 observational studies, OR=0.59; 95% CI = 0.43-0.81; 30 days: 10 observational studies, OR=0.47; 95% CI = 0.31-0.71) not serious not serious not serious serious none LOW	31 observational studies ONLY DESCRIPTIVE	8 observational studies ONLY	**FFP:RBC <1:1 vs 1:1** (24 hours: 6 observational studies and 1 RT, OR=2.05; 95% CI = 1.55-2.71; 30 days: 5 observational studies and 2 RCTs, OR=1.36; 95% CI = 1.09-1.69) **FFP:RBC <1:1.5 vs 1:1.5** (24 hours: 4 observational studies, OR=3.97; 95% CI = 1.37-11.49; 30 days: 5 observational studies, OR=2.45; 95% CI = 1.14-5.25) **FFP:RBC <1:2 vs 1:2** (24 hours: 9 observational studies, OR=2.85; 95% CI = 2.14-3.81; 30 days: 14 observational studies, OR=1.77; 95% CI = 1.50-2.10) not serious not serious not serious serious not serious LOW	not assessed

SR identification		SR	Luz 2019	Rodríguez 2020	Poole 2016	Rahouma 2018	Writz 2020
		characteristics	55 (2 trial and 53 observational), search up to July 31, 2018	33 studies (2 clinical trials and 31 observational studies); search between the first week of 1990 and week 40 of 2019	9 observational studies; search date December 14 2014	36 stidies (2 trials, 24 observational); search up to January 10th, 2016	39 (6 trial and 33 observational), search up to
		EVIDENCE			DESCRIPTIVE		
	2	**Health related-quality of life** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed		not assessed	not assessed
	3	**Length of ICU stay** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed	not assessed	not assessed	not assessed

		SR	**Luz 2019**	**Rodríguez 2020**	**Poole 2016**	**Rahouma 2018**	**Writz 2020**
SR identification		characteristics	55 (2 trial and 53 observational), search up to July 31, 2018	33 studies (2 clinical trials and 31 observational studies); search between the first week of 1990 and week 40 of 2019	9 observational studies; search date December 14 2014	36 stidies (2 trials, 24 observational); search up to January 10th, 2016	39 (6 trial and 33 observational), search up to
important	4	**Adverse effects** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed	not assessed	**Acute respiratory distress syndrome**: 6 observational studies and 2 RCTs (OR: 0.68, CI 0.40-1.16). **Acute lung injury**: 1 observational study and 1 RCT (OR: 1.23, CI 0.81-1.86). not serious serious not serious not serious not serious LOW	**Thromboembolic events**: 2 observational studies and 1 RCT (OR, 1.34; 95% CI, 0.28-1.56). serious serious not serious not serious not serious LOW
	5	**Acute transfusion reaction** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed	not assessed	not assessed	not assessed

SR identification		SR	Luz 2019	Rodríguez 2020	Poole 2016	Rahouma 2018	Writz 2020
		characteristics	55 (2 trial and 53 observational), search up to July 31, 2018	33 studies (2 clinical trials and 31 observational studies); search between the first week of 1990 and week 40 of 2019	9 observational studies; search date December 14 2014	36 stidies (2 trials, 24 observational); search up to January 10th, 2016	39 (6 trial and 33 observational), search up to
	1	**Time to definitive control of haemorrhage** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed	not assessed	not assessed	not assessed
	2	**Patient-reported outcomes** risk of bias imprecision indirectness inconsistency publication bias **QUALITY of EVIDENCE**	not assessed	not assessed	not assessed	not assessed	not assessed

	Pediatric population: Observational studies	
1a	**Mortality at 24 hours**	
	Low (<1:2) and high (≥1:2)	**Cannon 2017, Sehdev 2020** aRR 1.53 (95% confidence [CI] = 0.84–2.77; I2 = 0%, P =0.16).
	risk of bias	not serious
	imprecision	serious
	indirectness	not serious
	inconsistency	not serious
	publication bias	none
	Large magnitude of effect	none
	Dose-response gradient	none
	Residual confounding	none
	QUALITY of EVIDENCE	**LOW**
	FFP:PRBC: low (<1:2), medium (≥1:2 & <1:1), and high (≥1:1)	**Butler 2019** High vs low: aRR 0.49 (95% confidence [CI] = 0.27–0.89). Medium vs low: aRR 0.60 (95% confidence [CI] = 0.39–0.92).
	risk of bias	not serious
	imprecision	not serious
	indirectness	not serious
	inconsistency	not serious
	publication bias	none
	Large magnitude of effect	none
	Dose-response gradient	none
	Residual confounding	all plausible residual confounding would reduce the demonstrated effect
	QUALITY of EVIDENCE	**LOW**
1b	**Mortality at long term (30 days/1month and 12 months)**	not assessed
	QUALITY of EVIDENCE	
2	**Health related quality of life**	not assessed
	QUALITY of EVIDENCE	
	Pediatric population: Observational studies	**Sehdev 2020** **Nederpelt 2019** **Cannon 2017** **Butler 2019** **Cunningham 2019**
3	**Length of intensive care stay**	ICU days, median (IQR): BR n=131, 5(13), UR n=98, vs UR 4(11) ICU LOS, mean (SD): 1:1; 12 (13); 1:2; 12 (15); 1:3; 10 (11); 1:4; 10 (13); 1:5; 7 (7); 1:6; 10 (12); 1:6+, 10 (11) ICU free days, median (IQR): Low ratio n=65, 24 (16-26); High ratio n=299, 22 (14-26) ICU length of stay, median (IQR): Low n=128, 12 (6-18); Med n=118, 10 (5-20); High n=90, 13 (7-18) ICU free days, median (IQR): Low n=163, 7 (0-19); Med n=176, 2 (0-21); High n=126, 12 (0-20)
	risk of bias	not serious

		not assessed
	QUALITY of EVIDENCE	
4	**Adverse effects**	not assessed
	QUALITY of EVIDENCE	
	Pediatric population: Observational study	**Butler 2019**
5	**Acute transfusion reaction**	No transfusion reactions in either groups.
	risk of bias	not serious
		not assessed
	QUALITY of EVIDENCE	
	Observational study	**Cunningham 2019**
1	**Time to definitive control of haemorrhage**	Hemorrhage control procedure: Low n=163, 56 (34); Med n=176, 98 (56); High n=126, 63 (50). Low vs High ratio: aOR 0.4 (95% CI 0.13-1.22) Med vs High aOR 1.10 (95% CI 0.46-2.56)
	risk of bias	not serious
	imprecision	serious
	indirectness	not serious
	inconsistency	not serious
	publication bias	none
	Large magnitude of effect	None
	Dose-response gradient	None
	Residual confounding	all plausible residual confounding would reduce the demonstrated effect
	QUALITY of EVIDENCE	**LOW**
2	**Patient-reported outcomes: return to normal activities psychological wellbeing)**	not assessed
	QUALITY of EVIDENCE	

Appendice E4 – Tabelle delle evidenze. Comparazione: whole blood vs component therapy

Criteri for Downgrade

risk of bias:
-1 high or unclear risk of selection (randomizzazione e allocazione) or outcome reporting bias
-2 high or unclear risk of selection (randomizzazione e allocazione) and outcome reporting bias

imprecision:
-1 events<200 or < 400 patients or confidence intervals crossed the line of no difference with plausible effects in favor to the experimental/group group or wide confidence intervals
-2 al least two of the above conditions

indirectness:
-1 for setting (e.g., in-hospital)
-2 for setting (e.g., in-hospital) and not enough information for PICO description (e.g., trauma and no-truama)

inconsistency:
-1 for statistical inconsistecy I^2 >75% or methodological inconsistency (e.g., RCT and observational studies pooled together)
-2 for statistical inconsistecy I^2 >90%

publication bias:
-1 If n studies>10 and the Sr did not investigate the publication bias
-2 If high risk of publication bias

Criteri per Upgrade (in addition for observational studies)

Large magnitude of effect: This is a result of a study or meta-analysis and should not be used as a quality criterion. Large magnitude of effect may imply a high risk of biased results rather than increased confidence in results

Dose-response gradient: often exists in studies assessing etiology of disease, but effectiveness of an intervention usually does not show a linear dose-response pattern

Residual confounding: would further support inferences regarding treatment effect If some plausible confounders have not been documented, there is no credible way to determine how adjusting these parameters would alter the effectiveness estimates.

Appendice E4. Summary of Findings - GRADE approach.

			McQuilten 2020	Crowe 2020	Cruciani 2020	Cotton 2013	Leeper 2020
		Study design	Systematic Review of RCTs 1 RCT – Cotton 2013	1 RCT(Cotton 2013), 11 observational	1 RCT (Cotton 2013), 6 observational	Randomized controllred trial	Observational study
critical	1a	**Mortality 24 h**	RR 1.13 (0.37-3.49), Anticipated absolute effects control 96 per 1000, intervention 12 more per 1000 (61 fewer to 239 more).	The fixed effects pooled OR 0.83 (95% confidence [CI] = 0.56–1.24). For 24-hour mortality, there was a small to moderate level of heterogeneity (I2 = 27.2%, P = 0.37).	Three studies (one RCT and two cohort studies). Twenty-four hour mortality did not differ significantly between WB and COMP recipients (OR 0.80; 95% CIs 0.40/1.59; p = 0.53; I2 = 56%). The results were much the same when the analyses were limited to observational studies alone for 24-h mortality, OR 0.84; 95% CIs 0.33/2.15.	RR 1.13 (0.37-3.49), Anticipated absolute effects control 96 per 1000, intervention 12 more per 1000 (61 fewer to 239 more).	not assessed
		risk of bias	Very serious	Very serious	Very serious	Very serious	
		imprecision	Very serious	Serious	Serious	Very serious	
		indirectness	Not serious	Not serious	Not serious	Not serious	
		inconsistency	Not serious	Serious	Serious	Not serious	
		publication bias	None	None	None	None	
		Other consideration		No	No		
		QUALITY of EVIDENCE	**VERY LOW**	**VERY LOW**	**VERY LOW**	**VERY LOW**	
	1b	**Mortality 30 days**	RR 1.42 (0.63-3.19), Anticipated absolute effects control 154 per 1000, intervention 65 more per 1000 (57 fewer to 337 more).	The DerSimonian and Laird random effects pooled OR for in-hospital/30-day mortality was 0.79 (95% CI = 0.49–1.31). Moderate to high degree of heterogeneity (I^2 = 87.3%, P = 0.37)	Thirty-day/in-hospital mortality was available from one RCT and six cohort studies. The effect size did not differ between WB and COMP recipients (OR 0.90: 95 CIs 0.62/1.30; p = 0.56: I2 = 56%).	RR 1.42 (0.63-3.19), Anticipated absolute effects control 154 per 1000, intervention 65 more per 1000 (57 fewer to 337 more).	not assessed

			McQuilten 2020	**Crowe 2020**	**Cruciani 2020**	**Cotton 2013**	**Leeper 2020**
		Study design	Systematic Review of RCTs 1 RCT – Cotton 2013	1 RCT(Cotton 2013), 11 observational	1 RCT (Cotton 2013), 6 observational	Randomized controllred trial	Observational study
		risk of bias	Very serious	Very serious	Very serious	Very serious	
		imprecision	Very serious	Serious	Serious	Very serious	
		indirectness	Not serious	Not serious	Not serious	Not serious	
		inconsistency	Not serious	Serious	Serious	Not serious	
		publication bias	None	None	None	None	
		Other consideration		No	No		
		QUALITY of EVIDENCE	**VERY LOW**	**VERY LOW**	**VERY LOW**		
	1c	**In hospital mortality**	not assessed	not assessed	not assessed	not assessed	Regarding additional clinical outcomes, there was no difference in rate of in-hospital death, functional disability, hospital LOS, ICU LOS, and ventilator days between the 2 groups (all P > 0.25).
							Not serious
							Very serious
							Not serious
							Not serious
							None
							No
		QUALITY of EVIDENCE					**VERY LOW**
	2	**Health related-quality of life**	not assessed	not assessed	not assessed	not assessed	Regarding additional clinical outcomes, there was no difference in rate of in-hospital death, functional disability, hospital LOS, ICU LOS, and ventilator days between the 2 groups (all P > 0.25).
		risk of bias					Not serious
		imprecision					Very serious
		indirectness					Not serious

			McQuilten 2020	Crowe 2020	Cruciani 2020	Cotton 2013	Leeper 2020
		Study design	Systematic Review of RCTs 1 RCT – Cotton 2013	1 RCT(Cotton 2013), 11 observational	1 RCT (Cotton 2013), 6 observational	Randomized controllred trial	Observational study
		inconsistency					Not serious
		publication bias					None
		Other consideration					No
		QUALITY of EVIDENCE					**VERY LOW**
	3	**Lenght of intensive care stay**	not assessed	not assessed	not assessed	When comparing length of stay between WB and COMP subjects, there were no differences (median 30 days, IQR of 11 and 30 vs 29 days, IQR of 17 and 30; P = 0.89),	Regarding additional clinical outcomes, there was no difference in rate of in-hospital death, functional disability, hospital LOS, ICU LOS, and ventilator days between the 2 groups (all P > 0.25).
		risk of bias				Very serious	Not serious
		imprecision				Very serious	Very serious
		indirectness				Not serious	Not serious
		inconsistency				Not serious	Not serious
		publication bias				None	None
		Other consideration					No
		QUALITY of EVIDENCE				**VERY LOW**	**VERY LOW**
	4	**Adverse effects**	Not assessed	not assessed	One study reported a higher proportion of acute respiratory distress syndrome (ARDS), but not of multi-organ failure syndrome, infection, and embolic event, in WB recipients compared to COMP. (Perkins et al. 2011)	With respect to complications between mWB and COMP subjects, there were no differences in adult respiratory distress syndrome (0.0% vs 1.9%, P = 0.32), infectious complications (20% vs 17%, P = 0.72), severe sepsis/septic shock (4.5% vs 2.0%, P = 0.35), acute kidney injury/acute renal failure (2.0% vs 1.5%, P = 0.53), multiple organ	not assessed

			McQuilten 2020	**Crowe 2020**	**Cruciani 2020**	**Cotton 2013**	**Leeper 2020**
		Study design	Systematic Review of RCTs 1 RCT – Cotton 2013	1 RCT(Cotton 2013), 11 observational	1 RCT (Cotton 2013), 6 observational	Randomized controllred trial	Observational study
						failure (7.6% vs 9.0%, P = 0.79), or abdominal compartment syndrome (1.8% vs 1.9%, P = 0.97).	
		risk of bias			Very serious	Very serious	
		imprecision			Serious	Very serious	
		indirectness			Not serious	Not serious	
		inconsistency			Serious	Not serious	
		publication bias			None	None	
		Other consideration			No		
		QUALITY of EVIDENCE			**VERY LOW**	**VERY LOW**	
	5	**Acute transfusion reaction**	not assessed	not assessed	Two transfusion reactions recorded in COMP recipients, none in LOTWB recipients.	With respect to complications between mWB and COMP subjects, there were no differences There were no cases of transfusion-related acute lung injury in either group.	not assessed
		risk of bias			Very serious	Very serious	
		imprecision			Serious	Very serious	
		indirectness			Not serious	Not serious	
		inconsistency			Serious	Not serious	
		publication bias			None	None	
		Other consideration			No		
		QUALITY of EVIDENCE			**VERY LOW**	**VERY LOW**	
	2	**Time to definitive control of haemorrhage**	not assessed	not assessed	not assessed	not assessed	The whole blood group had faster time to resolution of base deficit [median (IQR) 2 (1–2.5) hours vs 6 (2–24) hours, respectively; P < 0.001].

			McQuilten 2020	**Crowe 2020**	**Cruciani 2020**	**Cotton 2013**	**Leeper 2020**
		Study design	Systematic Review of RCTs 1 RCT – Cotton 2013	1 RCT(Cotton 2013), 11 observational	1 RCT (Cotton 2013), 6 observational	Randomized controllred trial	Observational study
		risk of bias					Not serious
		imprecision					Very serious
		indirectness					Not serious
		inconsistency					Not serious
		publication bias					None
		Other publication					No
		QUALITY of EVIDENCE					**VERY LOW**
	3	**Patient-reported outcomes**	not assessed	not assessed	not assessed	not assessed	not assessed
		risk of bias					
		imprecision					
		indirectness					
		inconsistency					
		publication bias					
		QUALITY of EVIDENCE					

Appendice F – Costi e valutazioni economiche.

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

INDICE

COSTI

È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 40 records. Di questi sono stati esclusi tutti i lavori: (1) che non riportavano esplicitamente analisi dei costi intese come metodologia di identificazione, misurazione e valorizzazione delle risorse assorbite; (2) che fossero concentrati su prestazioni sanitarie non inerenti il trauma (ad esempio chirurgia vascolare, cardiochirurgia, trapianti, eccetera). Sono stati inclusi nella presente revisione 8 articoli inerenti la valutazione dei costi che (1) fossero relativi specificamente all'area traumatologica o (2) si concentrassero sui costi della produzione del plasma senza specificare la tipologia di erogazione della prestazione sanitaria. Oltre alla sezione dei costi unitari riportati dalla linea guida NICE NG39 (NICE 2016), si descrivono i costi riportati da 6 studi derivanti dalla search strategy. Di questi 6 (Campbell 2015, Ngwenya 2017, Callcut 2020, Shanders 2010, Shanders 2016, Abraham 2012) sono relativi a diversi contesti internazionali, e due riportano dati italiani (Martina 2003 e Nardi 2015). Dalla letteratura grigia, inoltre, sono state reperite anche ulteriori informazioni relative al contesto italiano (Figura 1).

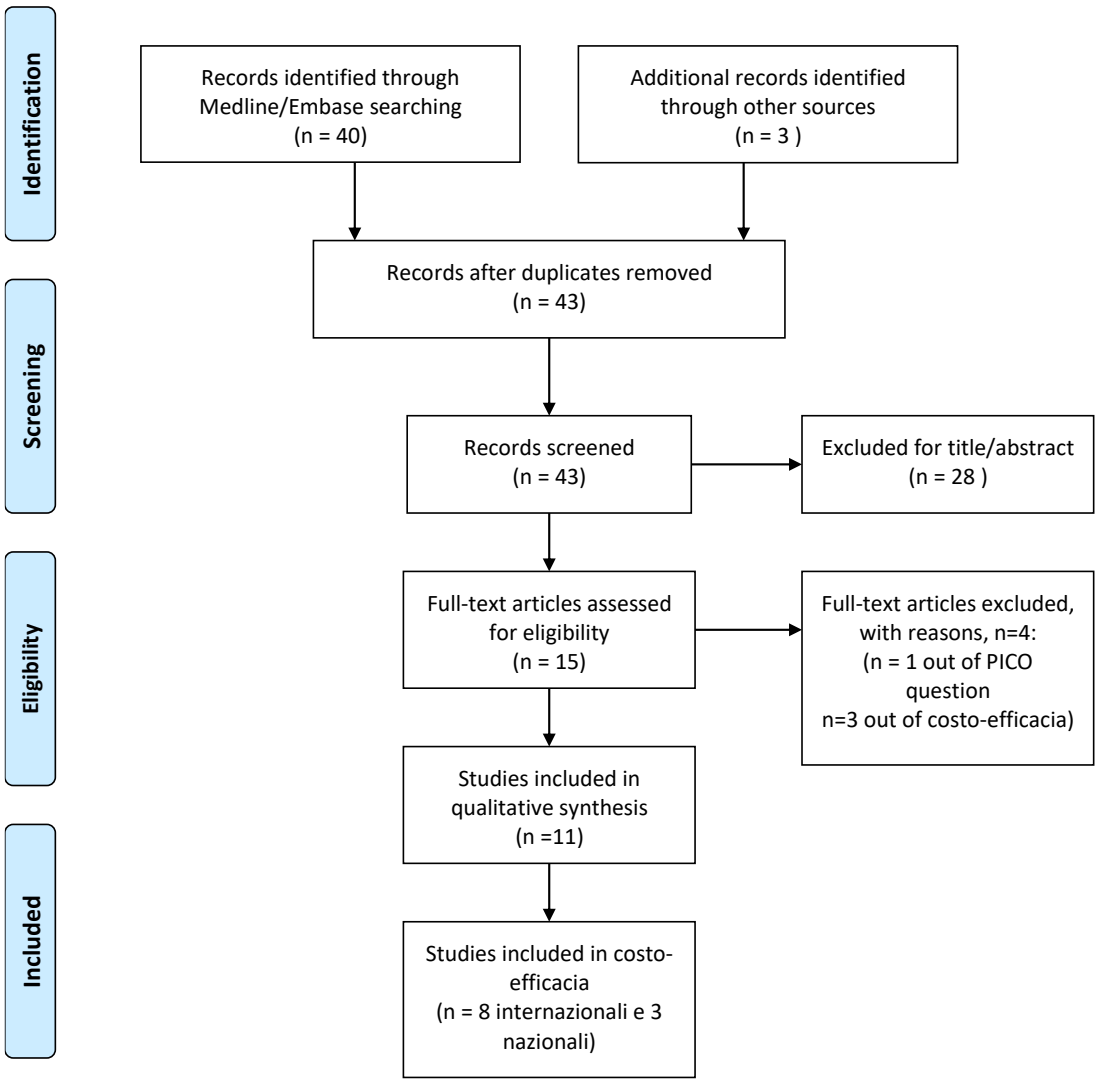


Figura 1. Flow diagram revisione della letteratura analisi dei costi

Contesto internazionale

La conoscenza dettagliata dei costi delle emorragie severe nel trauma è essenziale per una serie di parti interessate: i) per i responsabili dei servizi sanitari, comprendere i costi può aiutare a sviluppare strategie mirate di riduzione dei costi stessi; ii) per gli economisti sanitari, tali dati possono essere utilizzati come input negli studi che valutano la costo-efficacia di nuovi interventi di cessazione dell'emorragia; iii) per i pianificatori politici, l'onere dei costi a livello nazionale del trauma emorragico può essere confrontato con quello di altre condizioni e potenziali costi futuri (Campbell, 2015).
Dallo studio inglese di Campbell et al. si riportano in Tabella 1 i costi unitari degli emocomponenti e dei fluidi relativi agli anni 2012-2013, ricavati da fonti nazionali, utilizzati in prima istanza, ed integrati con costi locali quando necessario.

Tabella 1 - Costi unitari utilizzati per valutare i dati sull'utilizzo delle risorse TARN

Resource	**Unit cost UK £ 2012 to 2013**	**Source**
Blood components (per unit)		
PRBCs	£123.31	NHS Blood and Transplant Price List 2012 to 2013
FFP	£27.46	NHS Blood and Transplant Price List 2012 to 2013
Platelets	£209.30	NHS Blood and Transplant Price List 2012 to 2013
Cryoprecipitate	£189.19	NHS Blood and Transplant Price List 2012 to 2013
Transfusion laboratory issue cost	£2.00	Details available from the authors upon request
Fluids (500 mL)		
Colloids	£2.64	Finance Department, TARN participating hospital
Crystalloids	£0.71	Finance Department, TARN participating hospital
Hypertonic saline	£3.56	Finance Department, TARN participating hospital

In collaborazione con il Trauma Audit Research Network (TARN), ente indipendente di monitoraggio dell'assistenza ai traumi in Inghilterra e Galles, sono stati raccolti dal 1 aprile 2009 al 31 marzo 2011 dati dettagliati rispetto all'utilizzo delle risorse ospedaliere, all'assistenza estesa alla dimissione ospedaliera e alle riammissioni in ospedale fino a 12 mesi dopo l'infortunio, relativi a 441 pazienti adulti che consecutivamente si sono presentati in 22 ospedali (21 in Inghilterra, 1 in Galles) per traumi maggiori con emorragia severa. Così, lo studio si pone i seguenti obiettivi: i) generare stime delle risorse utilizzate dal paziente e dei costi sanitari, ii) esplorare se i costi variano tra particolari sottogruppi clinici e iii) rappresentare le cifre dei costi dal livello del paziente al livello nazionale per l'Inghilterra utilizzando i dati dell'Hospital Episode Statistics (HES). I costi a livello di paziente per il sistema sanitario britannico sono stati valutati rispetto ai costi espressi nel periodo 2012-2013 in Sterlina britannica. Poiché i fluidi IV sono forniti in sacche da 500 mL e 1 L, e gli emocomponenti come sacche unitarie, per entrambi sono stati calcolati gli sprechi (ad esempio se due unità e mezzo di PRBC sono stati trasfusi, è stato assegnato un costo di tre unità). Inoltre, a ciascuna unità di emocomponente trasfuso e sprecato è stato aggiunto il costo stimato del personale di laboratorio coinvolto nell'emissione dei componenti.
Dei 441 pazienti reclutati, l'80% presentava un trauma contusivo. Durante le prime 24 ore i pazienti hanno ricevuto una media di 9,87 (0,38) unità di PRBC e 4,92 (0,28) unità di FFP. Nessuna

complicazione dovuta alla trasfusione è stata riportata. I costi per i componenti del sangue rappresentano il 12% delle spese ospedaliere totali, per £2.362 (SE: £115) di cui il 70% (£1.656) attribuibile a PRBC e l'8% (£191) a FFP.
Inoltre, dalle analisi per sottogruppi sono emersi i seguenti risultati:

- i costi medi risultano significativamente triplicati nei pazienti che hanno richiesto una trasfusione massiva (£1,455 per PRBCs da 4 a 9 (n=294), £4,174 per PRBCs ≥ 10 (n=147));
- i costi medi risultano più elevati nei soggetti con ISS più elevato ((£1,615 per ISS < 15 (n=85), £2,540 per ISS ≥ 15 (n=356));
- i costi medi risultano leggermente più elevati nei soggetti con trauma penetrante (£2,270 per trauma contusivo (n=352), £2,7230 per trauma penetrante (n=89)).

Infine, lo studio stima che dei 49.859 casi di trauma maggiore osservati ogni anno in Inghilterra, 7.783 (15,6%) siano stati relativi a una grave emorragia, con costi associati stimati a £ 148.293.657, di cui il 32% dovuto a pazienti con una emorragia massiccia, per i quali il costo è stato stimato a £ 56.406.200.
Nello studio statunitense del 2018 di Ngwenya et al. è riportato che al San Francisco General Hospital (California, USA), il costo di 1 unità di PRBC era approssimativamente di $210 US. Questo costo includeva solo il prezzo del sangue proveniente dalla Croce Rossa, escludendo i costi associati all'approvvigionamento e al trasporto dei prodotti, alle fasi di lavorazione ospedaliera, al lavoro di laboratorio e i costi associati al personale e alle attrezzature necessarie per la trasfusione. Poiché questi costi operativi non erano disponibili presso l'istituzione, per la trasfusione chirurgica sono stati considerati i costi stimati negli Stati Uniti da Shander et al., che variavano da $726 a $1183 (in dollari del 2008) per unità PRBC trasfusa, i quali escludono i costi sostenuti a seguito del reclutamento di donatori, dei processi di raccolta del sangue e dei potenziali eventi avversi a lungo termine.
Inoltre, dall'analisi economica implementata per la Fase III del Trial americano PROPR (Holocomb, 2015), emerge che il costo unitario degli emocomponenti risulta pari a $230 per RBC; $65 per plasma, $575 per le piastrine e $55 per i crioprecipitati (Callcut 2020).
Si riportano, infine, i costi dalla Linea guida NICE NG39. Si noti che non è stato possibile determinare i costi del plasma liofilizzato e del plasma liquido, che non sono comunemente usati nella pratica clinica come il FFP (Tabella 2.).

Tabella 2. costi dalla Linea guida NICE NG39

Resource	Cost	Unit	Source
RBCs	£122	1 pack 220-300 ml per pack	NHS Blood and transplant price list 2014/15 [105]
FFP	£28	1 pack Mean: 271 ml (240-280 is common)	NHS Blood and transplant price list 2014/15
Crystalloids: • 0.9% Sodium Chloride • Hartmann's Solution • Plasmalyte M • Ringer's Lactate	 £0.70 £0.85 £0.91 £1.25	 1000-ml bag 1000-ml bag 1000-ml bag 500-ml bag	IV fluid guideline [98]

Source: Unit information sourced from GDG contact and internet.

Viene sottolineato che, poiché secondo le raccomandazioni del Dipartimento della Salute per i nati dopo il 01.01.96 si dovrebbero utilizzare particolari tipi di FFP e crioprecipitati che hanno subito ulteriori procedure per ridurre il rischio di virus, per i bambini, il FFP risulta sostanzialmente più costoso.

Dalla Linea guida NICE NG39 emerge, inoltre, che nell'uso degli emocomponenti possono sorgere problemi di fornitura e di spreco. Di fatto, per evitare di aspettare la corrispondenza incrociata tramite i test, ai pazienti viene principalmente assegnato il gruppo sanguigno del donatore universale, che potrebbe però scarseggiare. In più, per il FFP è richiesto un tempo di scongelamento, così alcuni importanti trauma centre possono avere una piccola quantità di plasma pre-scongelato che può far recuperare tempo in una situazione critica, tuttavia, il plasma pre-scongelato ha solo una durata di 24 ore e se non viene identificato un paziente idoneo per utilizzarlo, viene sprecato.
La Linea guida NICE NG39 evidenzia infine, come, oltre ai costi dei prodotti del sangue stessi, ci siano anche i costi di amministrazione derivanti dal laboratorio ospedaliero che deve preparare e rilasciare i prodotti, riportando il seguente esempio in Tabella 3.

Tabella 3. Linea guida NICE NG39 costi dei prodotti del sangue

	Cost	Components
Cost of group and save	£7.76	These costs include, but are not limited to: • Staff to receive the components, book into stock and place in controlled storage. • The running costs, maintenance, monitoring, mapping and repair of controlled storage devices. • Cost of remote blood fridges in theatres • The cost of the blood group and save sample plus consumables and reagents • The cost of selecting the blood, cross-matching, issue and labelling plus consumables and reagents • The annual cost of blood tracking devices • Staff costs • Lab costs (general) • Support for point of care • Training for theatre staff to use blood tracking kit • Training for blood administration competencies
Cost of cross-match (per unit)	£7.58	
Cost of issue of FFP (per unit)	£4.18	
Cost of issue cryoprecipitate	£3.51	
Cost of issue of platelets	£6.83	

Note these costs are from one particular hospital and may not be representative of all hospitals

Lo studio di Shander (2010), utilizza la tecnica della Activity based costing per stimare i costi delle trasfusioni in pazienti chirurgici in quattro ospedali degli Stati Uniti. La figura 2 mostra la differenza fra il costo di acquisizione ed il costo totale di produzione, del lavoro, dei materiali, delle attrezzature per produrre una unità di sangue. È evidente come esista una importante variabilità sia nel costo di acquisizione di un unità di sangue che nel Gap esistente fra costo di acquisizione e costo totale di produzione. Questo fa emergere l'importanza della ottimizzazione delle risorse impiegate per la produzione delle sacche di sangue in ogni setting ospedaliero, risultando quindi cruciale per il perseguimento dell'efficienza sia tecnica che allocativa, l'aspetto logistico e più in generale organizzativo. Per maggiore dettaglio si vedano i grafici riportati di sotto.

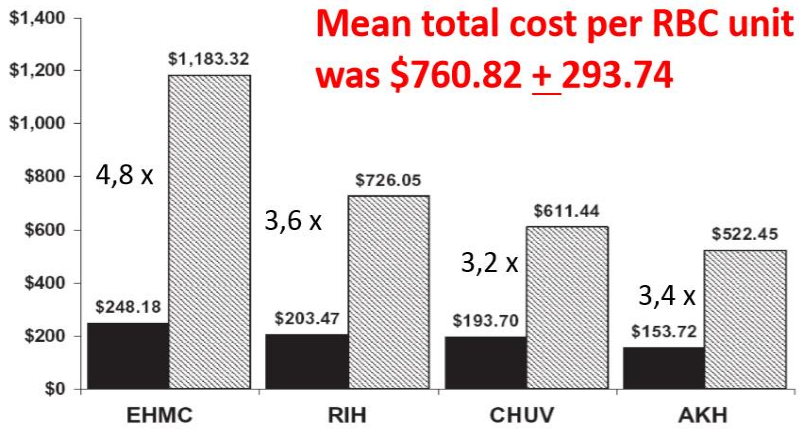


Fig. 2. Mean acquisition costs (■) and total ABC model costs (▨) per unit of blood. Mean per-unit acquisition costs included units that were wasted and additional services provided (e.g., irradiation, washing, cytomegalovirus testing) as described in the text. European currencies converted from the 1-year mean beginning May 2008 (CHUV conversion of $1 = SFr 1.12; AKH conversion of $1 = € 0.72).

Figura 2. Costi medi per Red Blood Cell Unit (da Shander et al. 2010)

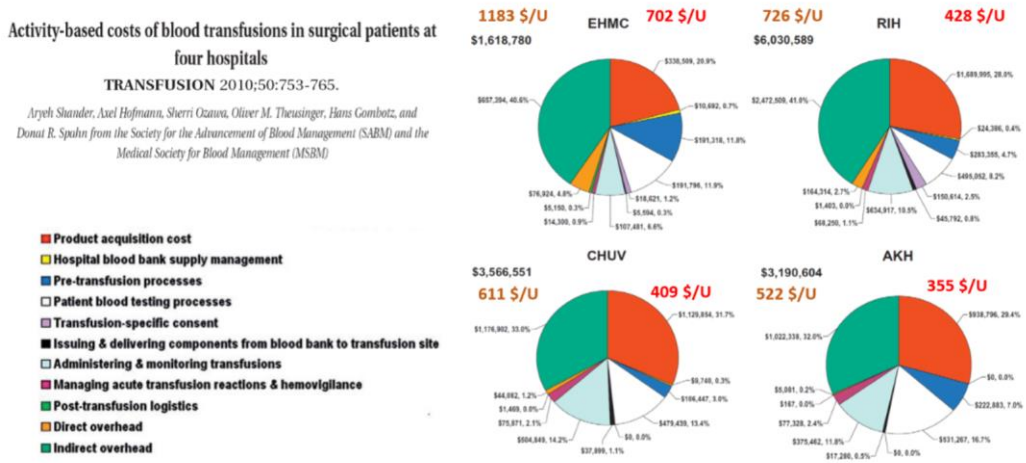


Figura 3. Dettaglio dei costi per unità di Red Blood Cell. (Da Shander et al. 2010)

In un successivo lavoro, Shander (2016) ha ripetuto la stessa analisi in un solo centro precedentemente incluso nel lavoro del 2010. La stima di costo di una unità di plasma fresco congelato di 200 ml è stata stimata in 41,95 dollari e cioè il 10,2% del costo totale di produzione (Figura 3).

Il lavoro di Abraham (2012), ha stimato il costo di due unità di Red Blood cell trasfuse in diversi centri dell'Europa Occidentale, attraverso una revisione sistematica della letteratura. Sono stati inclusi 6 studi relativi al Regno Unito, la Svezia, la Svizzera, l'Austria, e dalla Francia. Il costo totale di produzione stimato era di € 877,69.

Contesto Italiano

La tabella 4, relativa ad una presentazione riferita in letteratura grigia, riporta il costo degli emocomponenti in Italia.

Tabella 4. Costi emocomponenti in Italia

Costo degli emocomponenti in Italia

	Sino al 30 giugno 2016	Dal 1° Luglio 2016
Concentrato eritrocitario privato del buffy-coat	158	136
Concentrato eritrocitario leucodepleto filtrazione in linea	-	181
Concentrato eritrocitario leucodepleto da aferesi	210	187
Extras		
- Leucodeplezione med. filtrazione post-storage	40	21
- Grouppo 0, Rh neg per scorte ed emergenze	15	20
- Irradiazione	38	19
	Sino al 30 giugno 2016	Dal 1° Luglio 2016
Plasma fresco congelato da sangue intero	20	21
	Sino al 30 giugno 2016	Dal 1° Luglio 2016
Concentrato piastrinico da buffy-coat (procedura manuale)	115	97
Platelets pool from buffy-coat (procedura automatica)	--	207
Concentrato piastrinico da aferesi leucodepleto	438	418

Nessuno dei lavori scientifici inclusi riporta dati specifici riguardanti i costi del trauma. Il lavoro di Martina et al. (2003) stima il costo medio per tipologia di prestazione in 10 centri trasfusionali distribuiti sul territorio italiano. La metodologia è quella dell'activity based costing e, ai fini della stima del costo pieno, si avvale di report del controllo di gestione delle strutture incluse nello studio. I prodotti per cui è stato possibile effettuare una stima attendibile sono stati:

- Unità di plasma da aferesi;
- Unità di piastrine da aferesi;
- Unità di sangue intero.

le macro categorie di costi che sono state incluse, mediante criteri di imputazione, sono state:

1. Personale impiegato per la raccolta e la lavorazione del sangue (medici, infermieri, biologi, tecnici, amministrativi, ausiliari);
2. Materiale diagnostico (reagenti);
3. Altro materiale sanitario (sacche di sangue, kit per aferesi);
4. Materiale non sanitario (cancelleria e materiale economale vario);
5. Attrezzature;
6. Costi Generali per cui non era possibile compiere una imputazione diretta (amministrazioni, lavanderia, pulizia, utenze Generali ecc).

La tabella 5 riporta i costi ti ogni centro incluso nello studio risulta aver sostenuto sia per la plasmaferesi che per la piastrina feresi che per il sangue intero.

Tabella 5. Costi plasmaferesi, piastrinaferesi e sangue intero (da Martina et al., 2003)

Prodotto		Plasmaferesi (Euro)	Piastrinaferesi (Euro)	Sangue intero (Euro)
Centro	A	107,8	-	79,7
	B	177,3	525,9	108,0
	C	254,8	636,3	209,2
	D	123,3	-	111,5
	E	98,7	109,8	79,1
	F	230,2	305,7	199,7
	G	145,0	553,9	92,4
	H	180,6	273,2	177,2
	I	111,7	453,2	104,3
	L	109,2	-	130,3
Totale		153,9	285,8	129,1
IC *		114,5 - 193,2	107,8 - 463,8	94.3 - 164

Per la plasmaferesi è stata trovata una associazione parziale negativa fra volume di produzione e costo del personale sanitario e del materiale sanitario. La relazione e invece positiva per il costo dell'attrezzatura. Per le rimanenti voci di costo, così come per la piastrina feresi e il sangue intero, le correlazioni sono risultate statisticamente non significative. I risultati, sottoposti ad opportuni test, non supportano l'ipotesi di economie di scala o di specializzazione nella produzione di prodotti emoderivati. In generale la piastrinaferesi è risultata il prodotto più costoso, con un costo medio di 285,8 euro. La plasmaferesi ha un costo inferiore, pari a euro 153,9 mentre il sangue intero è il prodotto con il costo inferiore, pari a euro 129,1.

Il lavoro di Nardi (2015) riporta invece i costi rilevati durante il primo anno dall'introduzione di un protocollo di early coagulation in due centri italiani. I pazienti inclusi erano stati i trasfusi con almeno tre unità di PRBC nelle 24 ore successive all'incidente. È stata effettuata una analisi comparativa fra il 2011 e il 2013, anno di introduzione del nuovo protocollo.

Relativamente ai costi per unità di sangue la stima riportata è di € 186 per il PRBC, di € 60 per il plasma e di €115 per il PTL.

Le tabelle 6 e 7 mostrano la differenza nel consumo di unità fra 2011 e 2013 con i costi totali sostenuti per ogni anno. L'introduzione del nuovo protocollo ha comportato un risparmio di circa €76.000.

Tabella 6. Differenza consumo varie unità di plasma 2011- 2013. (Da Nardi et al., 2015)

Study year		3 U	4 to 5 U	6 to 7 U	8 to 10 U	>10 U
2011	Patients, n (%)	32 (25%)	39 (30%)	17 (13%)	10 (7%)	33 (25%)
	Average plasma units	3.4	4.2	5.4	8.3	22.1
	Plasma:PRBC ratio	1:1	1:1	0.8:1	1:1	1.2:1
2013	Patients, n (%)	25 (26%)	33 (34%)	10 (10%)	12 (13%)	16 (17%)
	Average plasma units	1.3	2.4	3.4	6.6	10.6
	Plasma:PRBC ratio	1:2.8	1:2	1:2	0.8:1	0.7:1

[a]PRBC, Packed red blood cells; PTL, Platelets.

Tabella 7. Differenza costi varie unità di plasma 2011- 2013. (Da Nardi et al., 2015)

		Estimated cost for 1 U	2011		2013	
			Units (N)	Overall	Units (N)	Overall
PRBC		€186	1,048	€194,928	625	€116,250
Plasma		€60	1,167	€70,020	405	€24,300
PTL		€115	538	€61,870	258	€29,670
	Overall			€326,818		€170,220
	Balance					−€156,598
Fibrinogen		€400 (1 g)	0	0	134 g	€53,600
POC tests			0	0		€26,663
Overall			0	0		+€80,263
	Balance					−€76,335

[a]POC, Point of care; PRBC, Packed red blood cells; PTL, Platelets.

Per quanto riguarda la letteratura grigia reperita, una presentazione del 2018 svolta da Inghilleri mostra l'impatto sui costi di un protocollo di Patient Blood management in orto traumatologia rispetto al protocollo tradizionale. La stima riporta come risultati relativi a trasfusioni di Red Blood cells di €161 a paziente nel gruppo Patient Blood management e di € 222 nel gruppo controllo.

COSTO-EFFICACIA

E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library (Figura 4). Sono stati individuati 34 records, da cui sono stati inclusi 4 studi (Ngwenya 2017, Callcut 2020, Caitlin 2014, Serrato-Avila 2018).

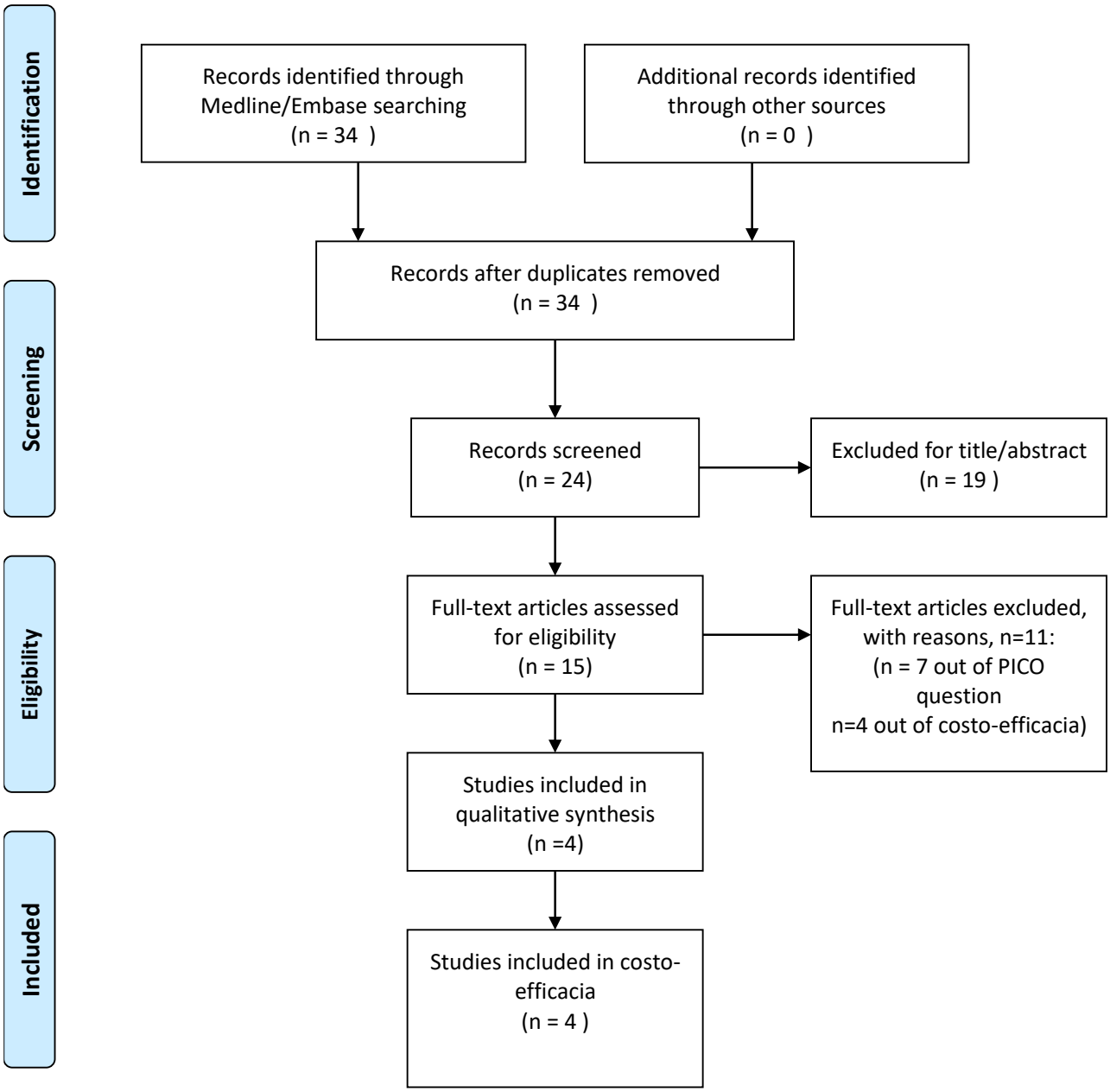


Figura 4. Flow diagram revisione della letteratura analisi costo-efficacia

In un centro traumatologico di livello I è stata così condotta un'analisi retrospettiva di pazienti con TBI ricoverati nell'unità di terapia intensiva del San Francisco General Hospital (California, USA) tra il gennaio 2011 e il settembre 2015, escludendo i pazienti di età inferiore a 16 anni e i deceduti entro 24 ore dall'ospedalizzazione, e confrontato i pazienti gestiti con un protocollo trasfusionale restrittivo (livello di emoglobina target >7 g/dl) rispetto a uno liberale (livello di emoglobina target >10 g/dl) (Ngwenya 2017). L'importo totale in dollari dei costi associati alla trasfusione per persona in ciascun gruppo trasfusionale è stato stimato moltiplicando il numero medio di unità PRBC trasfuso a persona per il costo di unità trasfusa.

Non è stata riscontrata alcuna differenza nei due gruppi di trasfusione per i giorni trascorsi in terapia intensiva (p = 0,21) o per i giorni sotto ventilazione meccanica (p=0,40). Tuttavia, la quantità di tempo con febbre è stata significativamente più bassa nel gruppo Hb 7-g/dl (p=0,01). La mortalità ospedaliera mostra tassi comparabili: 10,3% (101 pazienti) nel Gruppo Hb 10-g/dl e 8,4% (49 pazienti) nel gruppo Hb 7-g/dl. Utilizzando il range $726– $1183 (nel 2008 in dollari USA) per il costo medio per unità PRBC trasfusa, si è stimato che un paziente nel gruppo Hb 10-g/dl aveva costi associati alla trasfusione tra $1533 e $2499 rispetto a $1291– $2104 stimati per un paziente nel gruppo Hb 7-g/dl, dopo l'aggiustamento per l'inflazione al 2016. Dallo studio emerge così che la variazione della soglia di Hb da 10 a 7 g/dl faccia risparmiare dai $242 ai $394 per paziente. In particolare, tra i pazienti con un punteggio GCS ≤8, che avevano maggiori probabilità di ricevere una trasfusione, il risparmio per paziente è stato di $1049– $1710, e si suppone che a livello ospedaliero, dove vengono ammessi in terapia intensiva circa 30 pazienti con trauma cranico ogni mese, la modifica del protocollo faccia risparmiare tra $87.156 e $142.020 annualmente.

Lo studio dimostra quindi che l'adozione di un protocollo trasfusionale restrittivo sembra essere associato ad un minor numero di giorni di febbre, nessuna differenza nei tassi di mortalità ospedaliera e un risparmio medio di $115.000 annui.

Anche lo studio di Callcut et al. mostra un'analisi economica volta a quantificare i costi associati a due diverse strategie trasfusionali. Lo studio si riferisce ai risultati emersi dal Pragmatic,Randomized, Optimal Platelet and Plasma Ratios (PROPPR) trial (Holocomb, 2015), studio multisito (12 trauma center di primo livello nord-americani) randomizzato di Fase III su 680 soggetti, in cui è stata confrontata l'efficacia della trasfusione di plasma e piastrine e RBC nel rapporto 1:1:1 (n=338) rispetto al rapporto 1:1:2 (n=342). Lo studio è strutturato su un albero decisionale che ha l'obiettivo di proiettare e generalizzare i risultati del trial di riferimento.

L'analisi economica si concentra sui costi ospedalieri totali stimati nei primi 30 giorni di cura: per esaminare il costo e le conseguenze economiche nell'implementazione dei due protocolli trasfusionali (1:1:1 vs 1:1:2). Si sono così raccolti dati solo sull'utilizzo delle risorse durante il ricovero ospedaliero, e utilizzando i codici di procedura e diagnosi della classificazione internazionale delle malattie, nona revisione (ICD-9) sono stati stimati i costi per giorno di ricovero da un database statunitense che contiene i dati sui costi ospedalieri di tutti i pagatori. I costi trasfusionali sono stati valutati separatamente per ottenere costi marginali diretti per ogni intervento. Il costo unitario degli emocomponenti utilizzato per il calcolo risulta pari a $230 per RBC; $65 per plasma, $575 per le piastrine e $55 per i crioprecipitati.

Nelle prime 24 ore sono state utilizzate 25,5 unità di emocomponenti nel gruppo 1:1:1 rispetto a 19 unità nel gruppo 1:1:2. Considerando solo il costo attribuibile ai prodotti sanguigni, è emerso come il gruppo 1:1:1 mostrasse costi complessivi più elevati, ma con maggiori probabilità di raggiungere l'emostasi e la diminuzione della morte per emorragia entro 24 ore: il costo medio degli emocomponenti per i pazienti con protocollo 1:1:1 che hanno raggiunto l'emostasi e sono sopravvissuti 30 giorni sono stati $7662, rispetto a $4530 per quelli sul protocollo 1:1:2; per i pazienti deceduti entro 30 giorni i costi relativi agli emocomponenti erano più alti nel gruppo 1: 1: 1, e in particolare, per i pazienti deceduti prima di raggiungere l'emostasi, i costi medi del sangue erano $16.023 rispetto $9132.

Anche i costi ospedalieri sono risultati più elevati nel gruppo 1:1:1 per pazienti sopravvissuti dopo aver raggiunto l'emostasi, rispetto a 1:1:2 ($ 56.131 vs $ 54.590). Al contrario, i costi ospedalieri per i pazienti che inizialmente hanno raggiunto l'emostasi ma alla fine non sono sopravvissuti, o per i pazienti che non hanno mai raggiunto l'emostasi con conseguente morte, sono risultati inferiori nel gruppo 1:1:1 ($19.431 vs $25.255, $11,009 vs $10,830).

Il costo totale del sangue per 100 pazienti era di $934,883 per il protocollo 1:1:1 e di $584,744 per il protocollo 1:1:2, tuttavia per ogni 100 pazienti trattati nel gruppo 1:1:1, raggiungevano l'emostasi 8 pazienti in più rispetto al gruppo 1:1:2. L'ICER per questi pazienti che hanno raggiunto l'emostasi era di $43.634, pari alla differenza di costo divisa per la differenza di beneficio raggiunto dai due approcci.

A 30 giorni, il costo ospedaliero totale per 100 pazienti era circa $5,6 milioni nel gruppo 1:1:1 rispetto a $5,0 milioni nel gruppo 1:1:2. Per ogni sopravvissuto in più nel braccio di trattamento 1:1:1, l'ICER era di $91.324. Anche se questo gruppo è risultato più costoso, sono stati guadagnati 218,5 anni in più di aspettativa di vita. Quindi, utilizzando l'aspettativa di vita età specifica dei pazienti il e costo delle cure durante i 30 giorni di studio, il costo per anno di vita guadagnato è stato stimato per il gruppo 1:1:1 di $2994.

Gli effetti dei bracci di trattamento sono stati esaminati per sottogruppi tra cui il tipo di trauma, l'iniziale stato di alterazione mentale e la strutturale conferma di lesioni cerebrali traumatiche significative: l'ICER risulta leggermente migliore nel sottogruppo di pazienti con trauma penetrante, notevolmente migliorato per quelli con un punteggio GCS inferiore a 9 ($19.472 vs $43.634) e per i pazienti con un punteggio.

lo studio ha svolto anche un analisi di sensibilità multivariata tramite una simulazione di tipo Montecarlo che ha consentito di simulare l'impatto dell'incertezza sui risultati dello studio. L'analisi di sensibilità mostra come i risultati dello studio siano favorevoli a rapporto 1:1:1 nella maggioranza delle simulazioni. In particolare nel 38 % dei casi i risultati restituiscono a fronte di Maggiore efficacia anche un risparmio, mentre nel 48% dei casi i costi sono maggiori ma restituiscono un rapporto costo-efficacia favorevole.

In conclusione, il rapporto di trasfusione 1:1:1 nei pazienti con trauma emorragico severo è risultato una strategia conveniente per l'aumento dell'emostasi e la diminuzione delle morti per trauma.

Lo studio di Caitlin (2014) è relativo ad un'analisi di costo minimizzazione di due fluidi alternativi per la rianimazione di pazienti critici da trauma. Le due alternative in confronto erano 0,9% di sodio cloride e una soluzione bilanciata a base di elettroliti (plasma-lyte). Il modello è basato su risultati di efficacia provenienti da un trial randomizzato in doppio cieco che aveva confrontato i due trattamenti punto nello studio sono stati raccolti dati di laboratorio come ad esempio conta dei globuli, test di funzionalità epatica, studi di coagulazione, e valutazione della pressione arteriosa valutati al momento dell'arrivo in pronto soccorso. inoltre l'analisi ha incluso i costi per l'acquisizione dei fluidi e degli elettroliti, oltre al costo del personale infermieristico. Infine sono stati inclusi anche i costi dei materiali di consumo come l'alcol, i guanti e il kit di infusione. i dati relativi al tempo richiesto per preparare e somministrazione gli elettroliti non sono stati raccolti ma stimati da uno studio precedente a 4,6 minuti per infusione. I costi sono stati calcolati per paziente considerando i volumi medi di fluidi ricevuti la mediana di sostituzione degli elettroliti punto le concentrazioni media medie dissero di elettroliti a 6 ore e 24 ore sono stati confrontati con i pazienti che avevano ricevuto iniezione di 0,9 % di sodio cloride. L'ammontare mediano degli elettroliti somministrati nei due gruppi è stato confrontato. Le tabelle 7 e 8 mostrano i principali risultati nei due gruppi.

Tabella 8. Differenza consumo elettroliti (Da Caitlin et al., 2014)

Variable	0.9% Sodium Chloride Injection ($n = 24$)	Plasma-Lyte A ($n = 22$)	p^b
Mean ± S.D. concentration			
Magnesium, mg/dL			
6 hr	1.7 ± 0.40	2.0 ± 0.20	0.004
24 hr	2.0 ± 0.30	2.1 ± 0.24	0.24
Potassium, meq/L			
6 hr	4.0 ± 0.62	3.8 ± 0.49	0.22
24 hr	4.1 ± 0.52	4.2 ± 0.63	0.34
Calcium, mg/dL			
6 hr	7.9 ± 0.95	7.9 ± 1.28	0.82
24 hr	8.1 ± 0.54	8.3 ± 0.60	0.28
Phosphate, mg/dL			
6 hr	3.7 ± 1.01	3.0 ± 0.88	0.03
24 hr	3.2 ± 0.92	3.4 ± 0.96	0.59
Amount replaced within 24 hr, median (IQR)			
Magnesium, g	4.0 (2.5–4.0)	0 (0–2.0)	<0.001
Potassium, meq	0 (0–20)	5 (0–20)	0.49
Calcium, g	0.5 (0–3.0)	1.50 (0–5.25)	0.46
Phosphate, mmol	0	0	0.52
Patients receiving electrolyte replacement within 24 hr, no. (%)			
Magnesium	21 (87.5)	6 (27.3)	<0.001
Potassium	9 (37.5)	12 (54.5)	0.25
Calcium	12 (50)	12 (54.5)	0.76
Phosphate	1 (4.2)	2 (9.1)	0.60

[a]IQR = interquartile range.
[b]Calculated via chi-square test, Student's *t* test, or Wilcoxon rank sum test.

Tabella 9. Differenza costi somministrazione magnesio (da Caitlin et al., 2014)

	0.9% Sodium Chloride Injection ($n = 24$)			
	Cost ($) Including Labor		Cost ($) Excluding Labor	
Expense Item	Administration of 2 g Magnesium	Administration of 4 g Magnesium	Administration of 4 g Magnesium	Plasma-Lyte A ($n = 22$)
Mean ± S.D. resuscitation fluid cost (per 24 hr)[a]	7.65 ± 4.92	7.65 ± 4.92	7.65 ± 4.92	20.46 ± 12.94[b]
Safety syringe with attached needle (1 unit)	0.72[b]	0.72[b]	0.72[b]	0.00
0.9% sodium chloride i.v. flush, 10 mL	1.34[b]	1.34[b]	1.34[b]	0.00
Surgical gloves (pair)	0.17[b]	0.17[b]	0.17[b]	0.00
Tubing (single tubing)	1.82[b]	1.82[b]	1.82[b]	0.00
Alcohol wipes (per swab)	0.01[b]	0.01[b]	0.01[b]	0.00
Drug acquisition cost	6.77[b]	13.54	13.54[b]	0.00
Labor cost (for average)[d]	7.56[b,c]	7.56[b,c]	...[d]	...
Total (per 24 hr)	26.04	32.81	25.25	20.46

[a]Based on obfuscated threshold cost of $0.85/L for 0.9% sodium chloride injection and $2/L for Plasma-Lyte A.
[b]Cost reflects administration of two 2-g doses of magnesium sulfate, which is the common practice for magnesium replacement at the study site.
[c]Calculated using U.S. Bureau of Labor Statistics data on mean nurse compensation in California; assumes mean nursing time of 9.2 minutes (4.6 minutes per infusion).
[d]Not applicable.

I pazienti nei due gruppi non differivano in modo significativo rispetto a età, sesso, gravità del trauma, e indicatori di baseline derivati da esami di laboratorio. Non c'erano differenze significative nel volume di fluido infuso durante le prime 6 e le prime 24 ore. non venivano rilevate neanche differenze negli outcome critici come ad esempio la mortalità, la funzionalità renale, e altri parametri clinici. Come mostrato nelle tabelle 8 e 9 a 6 ore la concentrazione media di magnesio era significativamente più bassa con l'uso dello sodio clorite allo 0,9% in confronto con il plasma-lyte lo studio non riporta alcuna evidenza relativa ad analisi di sensibilità, inoltre non contestualizza l'analisi all'interno di una storia naturale della patologia, che adotti un orizzonte pluriennale e consideri anche eventuali complicanze.

Lo studio di Serrato – Avila (2018) considera un composto gelatinoso come alternativa costo efficace ad altri agenti emostatici. la gelatina può essere preparata in sala operatoria all'inizio della procedura chirurgica da un infermiere o da un chirurgo assistente. Lo studio mostra i materiali necessari a produrre 10 mm del composto: pasta gelatinosa, siringhe, aghi, pompa, catetere intravascolare.

Lo studio riporta un costo inferiore tra le 16 e le 28 volte rispetto alle alternative, tuttavia non riporta dati di efficacia, né un'analisi incrementale volta a stimare un rapporto costo-efficacia.

VALUTAZIONE DELLA QUALITA' DELLE EVIDENZE

Nota metodologica

La valutazione della qualità delle evidenze di costo-efficacia è stata condotta a due livelli.

In prima analisi è stata applicata la checklist CHEERS - Consolidated Health Economics Evaluations Reporting Standards- (Husereau 2013) per una valutazione del reporting metodologico degli studi. In secondo luogo è stata applicata la checklist per la valutazione della generalizzabilità (Drummond, 2005; Ruggeri, 2015) dei risultati ottenuti.

L'analisi della generalizzabilità può dar luogo a tre tipi di risultati diversi:

1. Analisi context-specific: nel caso in cui lo studio non rispetti più di due requisiti richiesti dalla checklist;
2. Analisi adattabile: nel caso in cui lo studio non rispetti un requisito richiesto dalla checklist;
3. Analisi generalizzabile: nel caso in cui lo studio rispetti tutti i requisiti richiesti dalla checklist.

Nel caso in cui ci si trovi in presenza di analisi adattabili, questo adattamento può essere condotto attraverso un'analisi bayesiana che trasformi i risultati dello studio in quantili di una distribuzione stocastica. Questa analisi dà luogo ad una distribuzione probabilistica che può essere interpretata come il livello di affidabilità dello studio rispetto al contesto di riferimento.

La costruzione dell'analisi stocastica avviene considerando i valori medi dei risultati costo efficacia degli studi ritenuti adattabili e le relative deviazioni standard, che servono a popolare una distribuzione di tipo *gamma*.

Risultati

Per quanto riguarda l'analisi della qualità del reporting due studi (Calcutt 2020 e Caitlin 2014) hanno riportato una valutazione della qualità medio-alta (75%). Lo studio di Ngwenya ha riportato un punteggio pari al 50%, mentre lo studio di Serrato-Avila (2018) del 37,5% (tabella 9).

In generale, nessuno degli studi ha riportato un indicatore di tipo costo per QALY, e non sempre di risorse utilizzate sono presentati separatamente rispetto ai costi unitari. Nessuno degli studi Adotta un orizzonte temporale pluriennale, per cui i risultati non sono proiettabili nel tempo. solo in un caso è riportata un analisi di sensibilità di tipo probabilistico, ma non sono presenti informazioni su come li distribuzioni statistiche siano state costruite e calibrate.

Per quanto riguarda la valutazione della generalizzabilità, nessuno degli studi è stato condotto in un setting italiano e nessuno degli studi può essere considerato trasferibile rispetto ad altri contesti. Infatti nessuno degli studi che sono basati su trials è multicentrico, gli outcome sanitari non sono espressi in termini di QALYs e la prospettiva è sempre ospedaliera, difficilmente quindi riconducibile ad altri contesti sia aziendali che giurisdizionali. Infine non è mai riportata informazione che possa ricondurre i risultati di efficacia ottenuti all'intera popolazione. In tabella 10 gli esiti del processo di generalizzabilità.

Per questi motivi si raccomanda di non utilizzare le evidenze di costo-efficacia reperite per compiere valutazioni in merito alla sostenibilità economica delle alternative di trattamento presentate nel contesto italiano.

Tabella 9. Valutazione della qualità metodologica degli articoli di costo-efficacia

SECTION/ITEM	CALLCUT ET AL. 2020	NGWENYA ET AL. 2017	CAITLIN ET AL. 2014	SERRATO-AVILA ET AL. 2018
TITLE AND ABSTRACT				
TITLE	1	0	1	1
ABSTRACT	1	1	1	1
INTRODUCTION				
BACKGROUND AND OBJECTIVES	1	1	1	1
METHODS				
TARGET POPULATION AND GROUPS	1	1	1	0
SETTING AND LOCATION	1	1	1	0
STUDY PERSPECTIVE	1	0	1	1
COMPARATORS	1	1	1	1
TIME HORIZON	1	0	1	0
DISCOUNT RATES	0	0	1	0
CHOICE OF HEALTH OUTCOMES	1	1	1	0
MEASUREMENT OF EFFECTIVENESS	1	1	1	0
MEASUREMENT AND EVALUATION OF PREFERENCE BASED OUTCOMES	0	0	0	0
ESTIMATING RESOURCES AND COST	0	0	1	0
CURRENCY AND CONVERSION	1	1	1	0
CHOICE OF MODEL	1	0	0	0
ASSUMPTIONS	1	0	0	0
ANALYTIC METHODS	1	0	1	1
RESULTS				
STUDY PARAMETERS	1	1	1	1
INCREMENTAL COSTS AND OUTCOMES	1	0	0	0
CHARACTERIZING UNCERTAINTY	0	0	0	0
CHARACTERIZING HETEROGENEITY	0	0	0	0
DISCUSSION				
STUDY FINDINGS, LIMITATIONS, GENERALIZABILITY, AND CURRENT KNOWLEDGE	1	1	1	0
OTHER				
SOURCE OF FUNDING	1	1	1	1
CONFLICT OF INTEREST	1	1	1	1
TOTAL	75,00%	50,00%	75,00 %	37,50%

Tabella 10. Valutazione della generalizzabilità delle evidenze economiche

ITEMS FOR GENERALIZABILITY	Callcut et al. 2020	Ngwenya et al.2017	Caitlin et al. 2014	Serrato-Avila et al. 2018
multicenter study (only for trial based)	na	0	0	0
context and description of the alternatives	1	1	1	1
complete reporting of the baseline characteristics of the study sample	1	1	0	1
adoption of a broad study perspective	0	0	0	0
clinical and cost data referring to the entire population	0	0	1	0
preference data relevant to the study populatiion	0	0	0	0
presence of quantitatiive/qualitative analyses perfored to evaluate the variability of results	0	0	0	0
clear justification of the model structure and parameters (only for models)	1	na	na	na
presence of a stochastic analysis to explore uncertainty (only for models)	1	na	na	na
reporting of epideiology (f relevant)	na	na	na	na
reported source of utility data	0	0	0	0
separate reporting of resources and unit costs	1	0	0	0
RESULT	context specific	context specific	context specific	context specific

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Appendice G – Metodi e criteri per la valutazione delle evidenze.

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

1. Definition of Clinical Questions

The clinical questions initially formulated by the authors of each working group and subsequently agreed were developed according to the PICOS method (Greenhalgh 1997, O'Connor 2008, Richardson 1995)
P: patients/ population characteristics
I: intervention on which the question is focused
C: comparison intervention / control /reference group
O: outcome measure relevant for the clinical question
S: study design on which to base the evidence search
The PICOS components of each prioritized question have been used by the Literature Group to define specific key words employed in comprehensive bibliographic searches.

2. Inclusion Criteria

Systematic reviews: In case of retrieval of many systematic reviews addressing the same PICOS question, in order to avoid repetition of the same information, double counting of primary studies and time consuming, only the best systematic review was considered. The criteria for select the best reviewwill be : the methodological quality of the review the update of the bibliographic search ,the level of overlapping of included primary studies, the quality of evidence coming from the included studies. The included reviews were the ones most updated, of better methodological quality and with higher quality of evidence and including the greater number of primary studies.
Primary studies: for each kind of question (effectiveness, diagnostic accuracy, acceptability and compliance, etc) a hierarchy of the study designs to be considered and inclusion/exclusion criteria was produced by the epidemiologists. For effectiveness questions randomised controlled trials were considered as the best source of evidence and searched in first instance using the following filter fro PubMed: "(Randomized Controlled Trial[ptyp]OR "Randomized Controlled Trial" [Title/Abstract]). The methodological quality assessment was also performed. Result of the bibliographic search and of the selection process made by the methodologists team will be sent to the clinical experts of the working group, who could suggest the inclusion of additional evidence or the exclusion of non relevant papers.

3. Risk of bias for included studies

The risk of bias of included studies will be assessed using the following validated checklist: Systematic review: AMSTAR CHECKLIST(Shea 2007);randomised controlled trials: criteria suggested by the Cochrane Handobook (Higgins 2011); cohort studies, case control studies and cross sectional surveis: Newcastle-Ottawa Scale (Wells 2010).

1. **Systematic review**: AMSTAR CHECKLIST. (Shea 2007).

2. **Randomized Controlled Trials**: criteria suggested by the Cochrane Handobook (Higgins 2011).

3. **Observational studies: cohort studies ,case control studies and cross sectional surveys**. criteria drawn from the Newcastle-Ottawa Scale (Wells 2010).

4. Grading the quality of evidence

The overall quality of evidence will be assessed using the GRADE approach (GRADE Working Group Website, Guyatt 2008).

HIGH quality of evidence: further research is very unlikely to change our confidence in the estimate of effect.

- Several high-quality studies (RCTs for treatment, cross sectional diagnostic accuracy studies for diagnosis) with consistent results
- In special cases: one large, high-quality multi-centre trial

MODERATE quality of evidence: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- One high-quality study
- Several studies with some limitations

LOW quality of evidence: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

- One or more studies with severe limitations

VERY LOW quality of evidence: Any estimate of effect is very uncertain.

- Expert opinion
- No direct research evidence
- One or more studies with very severe limitations

Factors that might decrease quality of evidence will be:

- Study limitations (risk of bias)
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias

Factors that might increase quality of evidence will be

- Large magnitude of effect
- Plausible confounding, which would reduce a demonstrated effect
- Dose-response gradient

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Appendice H – Accettabilità e Fattibilità

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

ACCETTABILITÀ

È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 535 records relativi all'accettabilità/fattibilità della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero. Sono state identificate 4 fonti per rispondere al dominio di interesse.
Con l'obiettivo di uniformare i protocolli internazionali, è stata istituita la campagna "**STOP the bleeding**" al fine di ridurre le morti traumatologiche dovute a sanguinamento (Albrecht 2017).
Popolazione pediatrica
Spesso gli adulti ricevono maggiori trasfusioni di sangue rispetto ai bambini, probabilmente dovuto al fatto che i **bambini** hanno una significativa riserva fisiologica che consente di tollerare una maggiore perdita di sangue prima che si renda necessaria una trasfusione (Lauby 2020).
I pazienti pediatrici, spesso vengono visitati per la prima volta dai basic life support (BLS) providers (combat medic) al confine, oppure la scelta dell'IDF advanced life support si riflette nell'utilizzo di una soluzione cristalloide. Ciò indica una deviazione dalle linee guida, probabilmente dovuta all'errata interpretazione rispetto alla natura innocua dei cristalloidi, convinzione sostenuta da molti fornitori (specialmente quelli addestrati nel sistema medico civile), che potrebbero anche essere riluttanti a somministrare FDP a pazienti pediatrici, dato che non sono disponibili linee guida specifiche sul dosaggio pediatrico (Nadler 2019).
Uno studio ha investigato la somministrazione preospedaliera di emoderivati destinata a pazienti pediatrici che hanno subito un trauma in **Iraq e Afghanistan,** mostrando come la componente maggiormente trasfusa fosse rappresentata dai globuli rossi (Lauby 2020).
Sebbene non vi sia alcuna ragione fisiologica per non utilizzare il sangue intero nei **bambini** con grave emorragia, è impegnativa la decisione di trasfondere sangue intero a un neonato a causa della scarsità di prove a sostegno dell'uso del sangue intero per i pazienti pediatrici e di linee guida per la rianimazione pediatrica, nonché il volume di LTOWB da trasfondere (Nadler 2020).
Si rende necessaria la formulazione di linee guida (Lauby 2020), protocolli di trattamento pediatrici e l'organizzazione delle competenze all'interno delle squadre mediche militari (Nadler 2019).

FATTIBILITÀ

È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 535 records relativi all'accettabilità/fattibilità della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero. Sono state identificate 19 fonti per rispondere al dominio di interesse.
La trasfusione massiva può essere facilmente implementata, sia nell'ambiente extra-ospedaliero che nella prima assistenza ospedaliera, la cui efficacia dipende dall'esperienza del personale che gestisce la rianimazione tramite valutazioni accurate e tempestive delle risorse, tempistiche e competenze (Shih 2019).

1. Protocolli di trasfusione massiva

Al fine di evitare una **eccessiva e non necessaria trasfusione** di componenti, è importante implementare una corretta strategia (Boutefnouchet 2015), da adattare localmente per conseguire i migliori risultati (Rossaint 2016). Ecco alcuni esempi.

- A **Singapore** i principali ospedali hanno implementato un **protocollo di trasfusione massiva nazionale**, vantaggioso per la pianificazione e la fornitura delle trasfusioni, dal punto di vista logistico ed operativo, adottando una terminologia ed un percorso comune. Ciò ha garantito una efficace comunicazione tra medici, banche del sangue ospedaliere e servizio nazionale di fornitura delle trasfusioni (Chay 2016).
- Nei **centri traumatologici tedeschi** è stato svolto un sondaggio, con più del 60% degli intervistati rappresentati da medici senior. Due terzi ha dichiarato di aderire ai protocolli di trattamento dei pazienti con trauma ed emorragia, inoltre, la metà degli intervistati dei centri traumatologici di livello II e III ha affermato di essere a favore dell'attuazione di un protocollo comune, come confermato da un quarto degli intervistati dei centri di livello I. Sono stati anche richiesti programmi di formazione interdisciplinare per migliorare la gestione del sanguinamento e della coagulopatia, mentre solo la metà ha richiesto l'adozione di una tecnologia avanzata (Albrech 2017).
- Infine, la survey realizzata dall'American Association for the Surgery of Trauma ha mostrato un'alta variabilità nella composizione delle trasfusioni massive (secondo il numero di unità di sangue, plasma e PLT), sottolineando una mancanza di standardizzazione (Etchill 2016).

È stato dimostrato come una previsione precoce accurata consenta l'ottimizzazione nell'utilizzo degli emocomponenti con riduzione gli sprechi. Lo studio di Weaver 2016, introduce la possibilità di attivare un 'codice rosso' o comunicazione dalla scena diretta all'ospedale dove sarà condotto il paziente, in modo da attivare efficacemente un protocollo trasfusionale massivo nel caso di sospetta emorragia maggiore, in modo che gli emoderivati siano immediatamente disponibili all'arrivo in ospedale, oltre che alla preparazione ad un possibile ed immediato intervento chirurgico. La decisione dovrà essere presa dal team medico / paramedico, anche nel setting pre-ospedaliero, considerando i dati clinici del paziente, quali i) sospetto o evidenza di emorragia attiva, ii) pressione arteriosa sistolica <90 mmHg, iii) mancata risposta a liquidi per via endovenosa (Weaver 2016).

2. Plasma

In generale, la trasfusione con freeze dried plasma (FDP), mostra un profilo di sicurezza potenzialmente favorevole (Sunde 2015), la cui praticità della trasfusione in ambito preospedaliero ne conferma la fattibilità (Shlaifer 2017).

Sulla scena del trauma potrebbe essere difficile avere immediatamente a disposizione sacche di plasma a causa delle tempistiche e del processo di scongelamento. Così l'uso di **plasma liquido** dovrebbe essere preso in considerazione data la migliore disponibilità e modalità di somministrazione (Hyatt 2019). Un recente studio ha dimostrato come una precoce rianimazione con liquid plasma possa ottimizzare l'aderenza alle linee guida del rapporto trasfusionale durante l'assistenza e portare a migliori risultati nei pazienti (come la riduzione del danno renale acuto) (Beattie 2020).

Setting militare

La cura preospedaliera dei traumi rimane una sfida per i traumi civili, in particolare se si verificano in località rurali remote, con risorse limitate e tempi di evacuazione prolungati. Tuttavia, i sistemi traumatologici più piccoli non hanno accesso a una fornitura di plasma o non dispongono di attrezzature adeguate per la conservazione e lo scongelamento, ostacolando così la capacità di utilizzo del plasma come fluido di rianimazione. Questa è ovviamente una sfida ancora più grande per i team preospedalieri, che non sono in grado di trasportare e utilizzare plasma fresco o scongelato sulla scena (Nadler 2019).

Il **plasma liofilizzato** sembra essere tatticamente vantaggioso poiché è più stabile senza refrigerazione, può essere trasportato dai medici e conservato sotto forma di (dried powder form) polvere secca (Davis 2017) e viene preferito rispetto al FFP perché stabile a diverse temperature, facile da trasportare e non richiede refrigerazione. Data la praticità e fattibilità, le forze armate statunitensi hanno liberalizzato l'uso del **FDP** prima della piena approvazione della FDA (Gurney 2018).

- Uno studio condotto in Israele, ha mostrato come in ciascuna compagnia di combattimento **Forward Medical Squad** sia stato inserito un medico o paramedico, diventato parte integrante dell'unità. L'esperienza con freeze dried plasma FDP ne ha dimostrato la fattibilità da parte dei paramedici in ambiente pre-ospedaliero e di combattimento (Benov 2016).

L'**Israel Defense Forces Medical Corps** (IDF-MC) ha adottato il plasma come fluido per la rianimazione preospedaliera, anche se esistono pochi o nessun dato sull'uso del plasma per pazienti pediatrici traumatizzati. I fornitori dell'IDF sono addestrati e attrezzati per fornire assistenza medica ai combattenti feriti e fornisce assistenza alla popolazione civile bisognosa nel settore di attività designato, specialmente nelle aree rurali remote che non dispongono di sistemi sanitari civili di emergenza, anche se gli strumenti pediatrici sono inclusi nell'armamentario, ma sono raramente trasportati e disponibili rispetto alle attrezzature per la popolazione adulta. Dato che i bambini vivono e giocano in zone di guerra e sono frequentemente trattati da personale medico militare, le linee guida dovrebbero includere indicazioni pediatriche specifiche (Nadler 2019).

3. Globuli rossi

La trasfusione di globuli rossi (RBC) è considerato un intervento salvavita in pazienti che presentano gravi emorragie e manifestano ipoperfusione o shock. In Finlandia, una unità **HEMS** (physician-staffed helicopter emergency medical service) ha implementato un protocollo per il trasporto preospedaliero di **globuli rossi**, mostrando come la procedura messa in atto da personale medico, sia fattibile, sicura e possa ridurre le tempistiche della trasfusione nei pazienti gravemente feriti o malati (Vuorinen 2020).

4. Sangue intero

Il **sangue intero**, può essere somministrata in modo sicuro a tutti i gruppi ABO utilizzando cold-stored low-titer O D+ blood (LTO+ WB) (Zhu 2019, Yazer 2016) e semplifica la rianimazione, grazie alla trasfusione di un'unica sacca rispetto alle quattro sacche generalmente somministrate (Yazer 2016, Yazer 2018). Il **sangue intero** ha una maggiore efficacia, sicurezza e vantaggi logistici sia per l'uso preospedaliero che ospedaliero.

Formazione/skills

In generale, i team preospedalieri di emergenza e traumatologici rappresentano gli unici gruppi in grado di somministrare sangue intero, sebbene ci siano programmi formativi dedicati ad altre specialità mediche e chirurgiche (trapianti, cardiaci, ecc.) (Zhu 2019). Un solido programma richiede un approccio multidisciplinare per questioni logistiche e pratiche poste dalla trasfusione del prodotto (Yazer 2018), una formazione clinica e amministrativa e una corretta gestione nella conservazione dello stesso, prevedendo il reclutamento di un numero sufficiente di donatori per garantire una costante accessibilità del prodotto (Zhu 2019). Un esempio, è il programma di formazione **Advanced Trauma Life Support** (ATLS) sviluppato dall'American College of Surgeons.

La procedura delle trasfusioni di LTOWB prevede corsi ad-hoc come l'**insegnamento** previsto nell'IDF (Israeli Defense Force) (Nadler 2020).

Setting militare

Le recenti guerre in **Iraq e Afghanistan** hanno rivalutato i potenziali benefici della rianimazione con WFWB nei pazienti con significativa emorragia (Katsura 2020). Difatti, all'inizio del conflitto in **Iraq**, le banche del sangue ambulanti sono state utilizzate per raccogliere WFWB warm fresh whole blood se l'insieme delle componenti non era disponibile (Vanderspurt 2019). Nel 2014, il **Tactical Combat Casualty Care Committee** degli Stati Uniti ha raccomandato il WB come prodotto ottimale per la rianimazione dei pazienti con shock emorragico traumatico (Vanderspurt 2019). Nonostante i dati promettenti e i potenziali benefici della WFWB in contesti traumatologici militari, ci sono stati rapporti limitati sull'uso della WFWB nella rianimazione di civili, in particolare in ambienti traumatologici austeri (Katsura 2020).

Un'alternativa efficace è rappresentata anche dal **cold-stored low-titer group O whole blood (LTOWB)** ben tollerato dato che conferisce un minor rischio di emolisi rispetto al plasma di tipo A e può essere trasfuso a pazienti di qualsiasi gruppo sanguigno ABO, riducendo le reazioni trasfusionali di incompatibilità ABO potenzialmente fatali. Clinicamente LTOWB: (1) è un prodotto più concentrato della rianimazione con componenti del sangue 1: 1: 1; (2) ha una migliore capacità di trasporto dell'ossigeno rispetto alla terapia con componenti del sangue; (3) ha un profilo di coagulazione del plasma migliore di FFP; e (4) ha le cold platelets che lo rendono più emostatico rispetto alle warm platelets con un rischio infettivo batterico inferiore (Vanderspurt 2019). CS-LTOWB vanta oltre un secolo di comprovata sicurezza; centinaia di migliaia di unità di CSLTOWB furono trasfuse durante le guerre del 20 ° secolo con poche reazioni avverse segnalate.

Mentre CS-LTOWB aumenta efficacemente la durata di conservazione del sangue intero (rispetto al WFWB che deve essere utilizzato entro 24 ore dalla donazione) e risulta logisticamente più semplice negli ambienti preospedalieri e non, una delle principali limitazioni del suo utilizzo è la corta durata di utilizzo dell'unità (Vanderspurt 2019). Attualmente, i medici delle **forze operative speciali** trasportano **LTOWB** in missioni selezionate, dato che la trasfusione di sangue intero nell'ambiente preospedaliero è sia fattibile che logisticamente valida (Gurney 2018). L'utilizzo di LTOWB facilita una rianimazione equilibrata nell'ambiente preospedaliero e la semplifica dato che non è più necessario il trasporto del paziente e la trasfusione di più sacche, con componenti del

sangue, in spazi ristretti, favorendo la logistica dell'operazione (con utilizzo di una singola sacca che alimenta simultaneamente tutte le componenti) (Nadler 2020). Tuttavia, poiché il **sangue intero** richiede la conservazione a freddo, l'uso è limitato a squadre mediche con accesso diretto alla refrigerazione e competenze nel trasporto di celle frigorifere (Nadler 2020), anche se più fattibile rispetto alla trasfusione bilanciata delle componenti che necessitano di un congelatore, un incubatore e uno scongelatore (Vanderspurt 2019).

- Dati i numerosi vantaggi logistici di **cold-stored LTOWB** negli ambienti preospedalieri e austeri del ruolo 2, è stata registrata una significativa richiesta del prodotto in CENTCOM US Central Command. Le risorse di trasporto limitate, la distanza e il pericolo derivante dal combattimento rendono poco pratica la spedizione dei prodotti sanguigni a un'unità di rifornimento di sangue per la ridistribuzione. Pertanto, la terapia trasfusionale CS-LTOWB appare essere fattibile e accettabile, nonostante la breve finestra di utilizzo una volta trasportata in CENTCOM, dato che: i) CS-LTOWB viene utilizzato nelle fasi iniziali delle rianimazioni, mentre nelle successive si somministrano componenti del sangue per condizioni specifiche, come FFP per la coagulopatia; e ii) la fornitura di CS-LTOWB appare essere limitata. CS-LTOWB ha rappresentato solo il 6,5% di tutti i prodotti trasfusi nel 2017 (2.176 unità su 33.481 unità totali) (Vanderspurt 2019).

Setting civile: In uno studio retrospettivo condotto a Okinawa, in Giappone, sono stati valutati i modelli e gli esiti nei pazienti che hanno ricevuto WFWB negli ultimi 20 anni, con particolare attenzione alla sicurezza e alla fattibilità dell'uso di WFWB nel contesto del trauma civile. I risultati suggeriscono come la rianimazione con WFWB sia sicura e fattibile in uno scenario di trauma civile austero. Tuttavia, si rendono necessari ulteriori studi prospettici per determinare se l'uso precoce di WFWB sia in grado di influenzare gli esiti trasfusionali, tra cui mortalità, volume totale trasfuso e costo del trattamento (Katsura 2020).

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Appendice I – Bibliografia degli studi inclusi.

CQ12. Gestione dell'emorragia. Miglior fluido per l'espansione volemica.

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