# Raccomandazioni 21-22 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

# SOMMARIO

## Lista delle raccomandazioni formulate

**Quesito 11:** Quali sono le strategie di rianimazione con fluidi più vantaggiose dal punto di vista clinico e della costo-efficacia nel paziente con trauma maggiore (ipotensiva vs. normotensiva)?

**Raccomandazione 21.** Nei pazienti con trauma ed instabilità emodinamica o shock e senza evidenza di trauma cranico si suggerisce una rianimazione volemica secondo una strategia di ipotensione permissiva (target PA sistolica 70 – 90 mmHg) fino al controllo definitivo dell'emorragia [Raccomandazione condizionata, qualità delle prove molto bassa].

**Raccomandazione 22.** Nei pazienti con trauma ed instabilità emodinamica o shock ed evidenza di trauma cranico moderato-severo non si raccomanda una rianimazione volemica secondo una strategia di ipotensione permissiva, ma un'infusione di fluidi con un obiettivo di pressione arteriosa più elevata (target PA sistolica 100-110 mmHg) [Raccomandazione forte, qualità delle prove molto 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 21 e 22:

- 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

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. 11

| **Quali sono le strategie di rianimazione con fluidi più vantaggiose dal punto di vista clinico e della costo-efficacia nel paziente con trauma maggiore (ipotensiva vs. normotensiva)?** | |
|---|---|
| **POPOLAZIONE:** | Bambini, giovani e adulti con emorragia acuta a seguito di un incidente traumatico. |
| **INTERVENTO:** | 1. Combinazione di ipotensione permissiva e normotensione.<br>2. Ipotensione permissiva. |
| **CONFRONTO:** | Rianimazione con normotensione come obiettivo durante le manovre di soccorso |
| **ESITI PRINCIPALI:** | **Critici**<br>Mortalità a 24 ore, 30 giorni / 1 mese e 12 mesi.<br>Qualità della vita.<br>Outcome neurologici<br>Durata della degenza in terapia intensive<br>Uso di emoderivati.<br><br>**Importanti**<br>Insufficienza multiorgano<br>Tempo per il controllo definitivo dell'emorragia ➔ *volume dell'emorragia*<br>Esiti riferiti dal paziente: dolore / disagio/ ritorno alle normali attività/ benessere psicologico. |
| **SETTING:** | Pre-ospedaliero (incluso il militare) e ospedaliero |
| **PROSPETTIVA:** | Popolazione, SSN:<br>• organizzazione ed erogazione de servizi per la gestione dei pazienti con trauma;<br>• rete regionale per il trauma;<br>• 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<br>○ Probabilmente no<br>○ Probabilmente si<br>● Si<br>○ Varia<br>○ Non so | Il 40% delle morti da trauma maggiore è imputabile all'emorragia non controllata, che rimane la principale causa di morte evitabile (Kauvar, Lefering et al. 2006, Alexandrescu, O'Brien et al. 2009). L'emorragia non controllata richiede una rapida identificazione con controllo della fonte emorragica ed un'azione immediata al fine di rianimare il paziente. Il recupero volemico con fluidi è il primo passo nella gestione emodinamica del paziente con shock emorragico: il ripristino parziale o totale della volemia può proteggere il paziente dalle conseguenze severe da shock ipovolemico (Cannon 2018).<br><br>Generalmente, la somministrazione dei fluidi in un paziente con emorragia in corso ha lo scopo di mantenere la circolazione e la perfusione degli organi. Tuttavia, un eccesso di fluidi potrebbe aumentare il rischio di coagulopatia e di edema tissutale con la conseguente alterazione della perfusione dei tessuti e complicanze come la sindrome compartimentale addominale o la sindrome da distress respiratorio acuto (Solomonov, Hirsh et al. 2000, Varela, Cohn et al. 2003, Srivastava 2017, Muttath, Annayappa Venkatesh et al. 2019). Il livello ottimale di pressione arteriosa da mantenere durante la rianimazione del paziente con shock emorragico è tuttavia ancora discusso.<br><br>Il recupero volemico con la rapida infusione intravenosa di fluidi sino ad ottenere una normalizzazione della pressione arteriosa è stata la strategia tradizionale di gestione dell'emorragia da trauma. Al contrario, più recentemente si è ipotizzato che limitare la quantità di fluidi somministrati con una strategia di "ipotensione permissiva" potrebbe migliorare gli esiti clinici del paziente con trauma in quanto ridurrebbe la perdita ematica dai focolai emorragici prima del loro controllo (Owattanapanich, Sirikun et al. 2018). Tuttavia, l'evidenza è ancora limitata e questa pratica potrebbe differire a seconda della tipologia di meccanismo traumatico (penetrante o contusivo) e di tipo di danno (presenza di trauma cranico). | |

## Effetti desiderabili

Quanto considerevoli sono gli effetti desiderabili attesi?

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ Irrilevanti<br>○ Piccoli<br>○ Moderati<br>● Grandi<br>○ Variano<br>○ Non so | E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati incluse 5 revisioni sistematiche (RS) di studi randomizzati e controllati (RCT), quasi-RCT e/o osservazionali (Tran, Yates et al. , Duan, Li et al. 2015, Albreiki, Voegeli et al. 2018, Owattanapanich, Sirikun et al. 2018, Safiejko, https://orcid.org et al. 2020), 2 studi randomizzati e controllati (Carrick Matthew, Morrison Catherine et al. , Schreiber, Meier et al. 2015) e 2 studi randomizzati e controllati ricavati dalla LG NICE sul trauma maggiore (Bickell, Wall et al. 1994, Dutton, Mackenzie et al. 2002).<br><br>Per analizzare l'evidenza proveniente da più RS che valutano gli stessi interventi (limited fluid resuscitation versus conventional resuscitation) per la stessa condizione (trauma maggiore con shock emorragico) ma con outcome clinici differenti è stata condotta una "overview di RS" al fine di comprendere tutti gli outcome critici ed importanti considerati. | |

*Osservando l' "overlapping" tra RS, gli studi randomizzati e controllati identificati dalla strategia di ricerca e dalla linea guida NICE sono inclusi nelle RS. Inoltre, anche l'overlapping dei PICO delle revisioni incluse risulta sovrapponibile.*

*Le RS presentano stessa popolazione ed interventi ma outcome differenti, perciò è stata adottata la metodologia delle "overview of reviews" per presentare la sintesi dell'evidenza delle 5 revisioni sistematiche incluse al fine di riportare in modo trasparente l'evidenza trovata e fornire evidenza rispetto a tutti gli outcome desiderabili e indesiderabili definiti critici e importanti.*

Le caratteristiche generali delle *5 revisioni sistematiche* sono riportate in modo completo **nell'Appendice B**. Nessuna RS comprende nei criteri di eligibilità il traumatic brain injury (TBI). Di seguito si riportano in tabella le caratteristiche principali.

| | **ALBREIKI 2017** | **DUAN 2015** | **OWATTANAPANICH 2018** | **SAFIEJKO 2020** | **TRAN 2018** |
|---|---|---|---|---|---|
| **NUMBER OF STUDIES** | 5 RCT and 5 observational studies, up to may 2016 | 11 RCT, up to january 2015 | 20 RCT, 4 observational studies up to january 2018 | 28 RCT and quasi-RCT*, up to june 2020 | 5 RCT, up to may 2017 |
| **POPULATION** | adult patients (aged ≥ 15 years) of blunt or penetrating trauma, with one or more documented episode of hypotension (systolic blood pressure ≤ 90 mmHg); | The trauma patients in the study presented with a common clinical syndrome - hemorrhagic shock | adult patients aged older than 18 years who had traumatic hemorrhagic shock and a systolic blood pressure below 90mmHg. | traumatic hemorrhagic shock patients | adult patients with penetrating or blunt traumatic injury and suspicion of hemorrhage. Civilian or military patient populations were both eligible. |
| **INTERVENTIONS** | normotensive and hypotensive trauma | fluid resuscitation | conventional fluid resuscitation with normotension (liberal fluid resuscitation) versus hypotensive resuscitation (limited fluid resuscitation). | hypotension versus conventional fluid resuscitation | permissive hypotension vs. conventional resuscitation |
| **SETTING (DECLARED IN INCLUSION CRITERIA) ➔ *EARLY C3*** | Mixed (pre hospital and in hospital) | no indication of clincial setting | Mixed (pre hospital and in hospital) | Mixed (pre hospital and in hospital) | Mixed (pre hospital and in hospital) |
| **STUDY DESIGN** | randomized and retrospective studies | randomized or quasi-randomized | randomized controlled trials (RCTs) and cohort studies | randomized controlled trials (RCTs) and quasi-randomized trials. | randomized controlled trials and quasi-randomized trials |

| | | | | | |
|---|---|---|---|---|---|
| **EXCLUSION CRITERIA** | traumatic brain injury (TBI) | traumatic brain injury (TBI) | pregnant or traumatic brain injuries (TBI) | Not reported | traumatic brain injury (TBI) |

*Quasi-RCT is defined by SR'authors, however some studies are defines as comparative cohort (observational )in other SRs

**Critical**

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

Tutte le revisioni sistematiche riportano dati relativi alla mortalità. Di seguito si riporta una tabella riassuntiva con gli effetti degli interventi di gestione dell'emorragia nel trauma. Vedi **Appendice C** per ulteriori dettagli.

| SYSTEMATIC REVIEW | NUMBER OF TRIALS | OUTCOME: MORTALITY |
|---|---|---|
| **ALBREIKI 2017** | **5 RCT** and **5 observational studies**, up to may 2016 | Data are described narratively. No meta-analysis was conducted.<br>Five RCTs reported data on mortality.<br>Among 1157 trauma patients resuscitated with low and large volumes of fluid mortality rates were 21.5% (123 deaths from 570 patients) and 28.6% (168 deaths from 587 patients), respectively.<br><br>The collective comparative studies that encompassed five RCTs and one prospective study showed that the pooled survival rate of limited versus liberal volume resuscitation was 82.9 and 80.2%, respectively. |
| **DUAN 2015** | **11 RCT**, up to January 2015 | Nine studies - 1,384 patients compared the mortality of hemorrhagic shock patients between limited fluid resuscitation (LFR) and regular fluid resuscitation (RFR).<br>Mortality for LFR group vs. RFR group was 131 of 675 (19.4%) vs. 208 of 709 (29.3%).<br>**The results indicated that limited fluid resuscitation may reduce the mortality in patients with hemorrhagic shock (RR = 0.67; 95% CI = 0.56-0.81; P < 0.0001; χ2 = 12.35; P = 0.14; I2 = 35%)) (Figure 2**).<br><br>SUBGROUP ANALYSIS FOR COUNTRY/ETHNICITY: 3 trials from America and 6 trials from China. The consequences of subgroup analysis were consistent with the total analysis. However, the difference of mortality between LFR and RFR groups in America descent was not significant as that in Asian descent. |
| **OWATTANAPANICH 2018** | **20 RCT**, 4 observational studies up to january 2018 | 24 studies, n = 1473;<br>RR: 0.50; 95% CI: 0.40– 0.61.<br>A mild heterogeneity among these 24 studies was observed (Q test: 0.11, which is greater than 0.1; I2: 27%) |
| **SAFIEJKO 2020** | **28 RCT and quasi-RCT***, up to june 2020 | Twenty-eight studies reported overall mortality.<br>Mortality with hypotension fluid resuscitation was 12.5% and was significantly lower than with the conventional fluid resuscitation group – 21.4% (RR = 0.58; 95% CI: 0.51–0.66; I2 = 37%; p < 0.001; Fig. 2).<br><br>In contrast, only one study indicated mortality rates during the first 24 hours. According to this study, mortality for hypotension versus conventional fluid resuscitation varied and amounted to |

| | | |
|---|---|---|
| | | 13.6% vs. 21.7% respectively (RR = 0.63; 95% CI: 0.25–1.58; p = 0.32). |
| **TRAN 2018** | **5 RCT**, up to may 2017 | Two studies presented 30-day mortality while three studies presented in-hospital mortality. In the meta-analysis using a random effects model, the permissive hypotension strategy demonstrated significant evidence of a survival benefit – a pooled odds ratio for mortality of 0.70 (95% CI 0.53 to 0.92). The $I^2$ statistic was 0%, suggesting minimal statistical heterogeneity. |

* Quasi-RCT is defined by SR'authors, however some studies are defines as comparative cohort (observational )in other SRs

**Health related quality of life**

Nessuna revisione considera l'outcome di interesse.

**Neurological outcome**

Nessuna revisione considera l'outcome di interesse.

**Length of intensive care stay (ICU)**

L'outcome di interesse è riportato da una sola revisione sistematica: Safiejko 2020.

Nella revisione di (Safiejko, Szarpak et al. 2020), due RCTs sono stati inclusi nell'analisi cumulativa.

L'analisi cumulativa mostra che non ci sono differenze statisticamente significative nella durata del ricovero in terapia intensiva tra chi è sottoposto a terapia ipotensiva e chi è sottoposto a trattamento convenzionale (MD = 0.38; 95% CI: –1.83–2.59; $I^2$ = 73%; p =0.74).

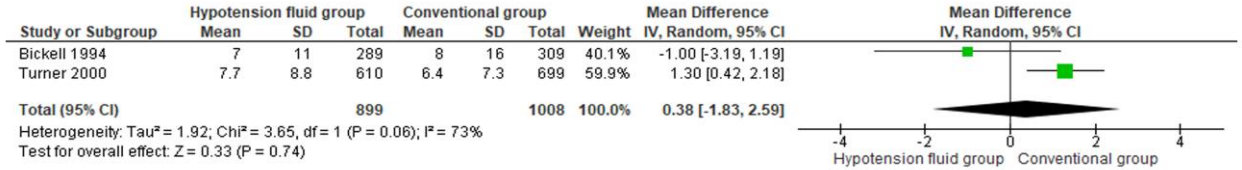


Figura 2. Forest plot of hypotension versus conventional fluid resuscitation, relative to length of intensive care stay.

Tre studi riportano la durata del ricovero ospedaliero. La differenza tra gruppi (hypotension vs conventional) non era statisticamente significativa (MD = –0.82; 95% CI: –2.43–0.78; $I^2$ = 0%; p = 0.32).

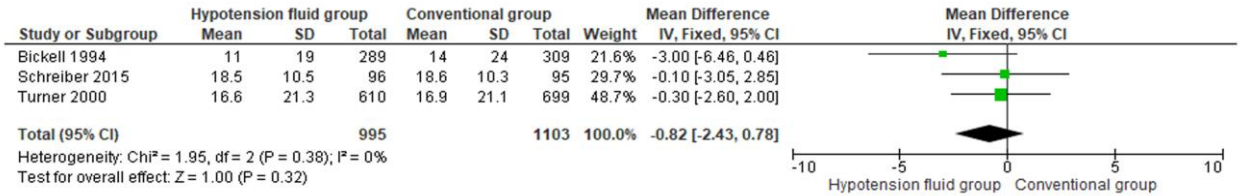


Figura 3. Forest plot of hypotension versus conventional fluid resuscitation, relative to length of hospital stay.

Vedi **Appendice C** per ulteriori dettagli.

**Blood products use**

Tra le 5 revisioni sistematiche incluse, 4 riportano i dati di interesse (Duan 2015, Owattanapanich 2018, Safiejko 2020, Tran 2018). Di queste RS, tutte riportano analisi quantitative, tranne Tran 2018 che identifica gli outcome "Globuli rossi concentrati e Cristalloidi" come secondari in una tabella descrittiva (vedi **Appendice C** per ulteriori dettagli).

- Piastrine (Duan 2015 e in Safiejko 2020)
- Globuli rossi concentrati (Owattanapanich 2018, Safiejko 2020, Tran 2018)
- Plasma fresco (Safiejko 2020)

| SYSTEMATIC REVIEW | NUMBER OF TRIALS | OUTCOME: BLOOD PRODUCT | | |
|---|---|---|---|---|
| | | **Piastrine** | **Globuli rossi concentrati** | **Plasma fresco** |
| **DUAN 2015** | **11 trials**, up to January 2015 | 4 trials , n = 856<br>MD 23.16 (95% CI 6.41 – 39.41)<br>$I^2$=63%<br>**The overall effect suggested that PLT value in LFR group was higher than that in RFR group (P = 0.007)** | | |
| **OWATTANAPANICH 2018** | **20 trials**, 4 observational studies up to january 2018 | | 3 trials, n=330<br><br>MD -132.09 (95% CI -203.08, -61.10<br><br>$I^2$=97% | |

| | | | | | |
|---|---|---|---|---|---|
| | | | The hypotensive resuscitation group had a lower amount of packed red cell transfusion than the<br><br>normotensive resuscitation group | | |
| | **SAFIEJKO 2020** | **28 trials**, up to june 2020 | 1 trial, n=74<br><br>(not included in Duan 2015)<br><br>MD 0.20 (95% CI -0.45, 0.85)<br><br>No difference between groups | 1 trail, n=74<br><br>(not included in Owattanapanich 2018)<br><br>MD 0.10 (95% IC<br><br>-1.56, 1.76)<br><br>No difference between groups | 1 trial, n=74<br><br>MD -0.10 (95% IC<br><br>– 0.92, 0.72)<br><br>No difference between groups |
| | **TRAN 2018** | **5 trials**, up to may 2017 | | No meta-analysis<br>See Appendix C for descriptive analyses | |

**Important:**

Time to definitive control of haemorrhage[1]

Tra le 5 revisioni sistematiche incluse, una revisione sistematica riporta propriamente l'outcome di interesse: Tran 2018. *Mentre come outcome surrogato Duan 2015 riporta dati inerenti tempo di Prothrombin (PT) e tempo activated partial thromboplastin (APTT)*. Di seguito si riportano le analisi relative. Vedi **Appendice C** per ulteriori dettagli.

[1] Explanatory not: coagulopatia prevention and lenght of active haemorrhage

| SYSTEMATIC REVIEW | NUMBER OF TRIALS | OUTCOMES | | |
|---|---|---|---|---|
| | | **length of active haemorrhage** | **Prothombin (PT)** | **Activated partial thromboplastin (APTT).** |
| **DUAN 2015** | **11 trials**, up to January 2015 | - | 4 trials, n= 931<br>MD -2.81 (95% CI -3.44, -2.17)<br>I2=79%<br>A favore della ipotensione permissiva | 3 trials, n= 856<br><br>MD -5.14 (95% CI -6.16, -4.12)<br><br>I2=0%<br><br>A favore della ipotensione permissiva |
| **TRAN 2018** | **5 trials**, up to may 2017 | 1 trials, n= 100 (Dutton 2002)<br>Hours: mean 2.57 +/- 1.46 in limited fluid resuscitation (SBP=70 mmHg) vs mean 2.97 +/- 1.75 conventional resuscitation (SBP=100 mmHg)<br>**No difference between groups** | | |

**Important:**

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

Nessuna revisione considera l'outcome di interesse.

## Effetti indesiderabili

Quanto considerevoli sono gli effetti indesiderabili attesi?

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ Grandi<br>● Moderati<br>○ Piccoli<br>○ Irrilevanti<br>○ Variano<br>○ Non so | E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati inclusi 5 revisioni sistematiche (RS) di studi randomizzati e controllati (RCT) (Tran, Yates et al. , Duan, Li et al. 2015, Albreiki, Voegeli et al. 2018, Owattanapanich, Sirikun et al. 2018, Safiejko, https://orcid.org et al. 2020), 2 studi randomizzati e controllati(Carrick Matthew, Morrison Catherine et al. , Schreiber, Meier et al. 2015) e 2 studi randomizzati e controllati ricavati dalla LG NICE sul trauma maggiore(Bickell, Wall et al. 1994, Dutton, Mackenzie et al. 2002) .<br><br>Osservando l'overlapping tra RS, gli studi randomizzati e controllati identificati dalla strategia di ricerca e dalla linea guida NICE sono inclusi nelle RS. Inoltre, l'overlapping dei PICO delle revisioni incluse risulta sovrapponibile.<br><br>Le RS presentano qualità metodologica simile, valutata tramite l'AMSTAR 2, perciò è stata adottata la metodologia delle "overview of reviews" per presentare la sintesi dell'evidenza delle 5 revisioni sistematiche incluse al fine di riportare in modo trasparente l'evidenza trovata e fornire evidenza rispetto a tutti gli outcome desiderabili e indesiderabili definiti critici e importanti.<br><br>**Multi organ failure**<br>Benchè l'ipoperfusione da rianimazione ipotensiva potrebbe scatenare / peggiorare una multiorgan failure, un solo studio ha evidenziato una maggiore incidenza di acute kidney injury nei pazienti sottoposti a questa strategia.<br>Tra le 5 revisioni sistematiche incluse, tre riportano l'outcome di interesse: Duan 2015, Owattanapanich 2018 e Safiejko 2020. Di seguito si riportano i dati relativi per ciascuna revisione sistematica. Vedi **Appendice C** per ulteriori dettagli. | Il panel ritiene che l'ipotensione permissiva dia effetti indesiderati gravi e non accettabili nei pazienti con TBI (ref. Brain trauma foundation 2000 etc.).<br>*Target pressorio consigliato da BTF 2019: PA sist 100-110 mmHg).* |

| SYSTEMATIC REVIEW | NUMBER OF TRIALS | MULTI ORGAN FAILURE |
|---|---|---|
| **DUAN 2015** | **11 trials**, up to January 2015 | 4 trials, n = 336<br>RR 0.37 (95% CI 0.21, 0.66)<br>$I^2$=0%<br><br>**limited fluid resuscitation may reduce the occurrence of multi organ failure in patients with hemorrhagic shock (P = 0.0008)** |
| **OWATTANAPANICH 2018** | **20 trials**, 4 observational studies up to january 2018 | 7 trials, n= 642<br>RR 0.40 (95% CI 0.26, 0.61)<br>$I^2$= 0%<br><br>In terms of the possible risks of this hypotensive strategy, 7 studies showed that the hypotensive resuscitation group had lower incidences of multi organ failure |

| | | | | |
|---|---|---|---|---|
| | **SAFIEJKO 2020** | **28 trials**, up to june 2020 | L'analisi cumulativa mostra che hypotension fluid resuscitation comparata alla conventional fluid resuscitation era associate a un più basso rischio di eventi avversi (10.8% vs. 13.4%, respectively; RR = 0.70; 95% CI: 0.59–0.83; $I^2$ = 52%; p < 0.001).<br><br>**L'uso della hypotension versus conventional fluid resuscitation mostra una più alta incidenza di anemia (74.3% vs. 68.6%), thrombocytopenia (33.6% vs. 29.4%) and acute renal failure (8.8% vs. 8.1%) (Tabella 1).** | |
| | **Nei pazienti con trauma cranico moderato-severo si ritengono possibili effetti indesiderati gravi da una rianimazione ipotensiva. La maggioranza degli studi ha, in effetti, escluso i pazienti con TBI, poiché l'ipotensione è uno dei fattori prognostici negativi più importanti nei pazienti con TBI in quanto causa di danno secondario.** | | | |

## Qualità delle prove

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

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ● Molto bassa<br>○ Bassa<br>○ Moderata<br>○ Alta<br>○ Nessuno studio incluso | La qualità delle prove complessivamente è molto bassa negli outcome considerati dalle revisioni sistematiche incluse (**Appendice E**). Per completezza, la qualità metodologica delle revisioni è stata effettuata e riportata in **Appendice D**. | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **CRITICAL** | | | | | **IMPORTANT** | | |
| | **SYSTEMATIC REVIEW** | **MORTALITY** | **HEALTH RELATED QUALITY OF LIFE** | **NEUROLOGICAL OUTCOMES** | **LENGHT OF STAY ICU** | **BLOOD PRODUCT USE** | **MULTIPLE ORGAN DISFUNCTION** | **TIME TO CONTROL HEMORRAGE** | **PATIENT REPORTED OUTCOME** |
| | **ALBREIKI 2017** AMSTAR II:LOW | Only descriptive synthesis | - | - | - | - | - | - | - |
| | **DUAN 2015** AMSTAR II:MODERATE | VERY LOW | - | - | - | VERY LOW | VERY LOW | PT : VERY LOW APTT: LOW | - |
| | **OWATTANAPANICH 2018** AMSTAR II:CRITICALLY LOW | VERY LOW | - | - | - | VERY LOW | VERY LOW | - | - |
| | **SAFIEJKO 2020** AMSTAR II:LOW | VERY LOW | - | - | VERY LOW | VERY LOW | VERY LOW | - | - |
| | **TRAN 2018** AMSTAR II:LOW | VERY LOW | - | - | - | Only descriptive synthesis | - | Only descriptive synthesis | - |

## Valori

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

| **GIUDIZI** | **RICERCA DELLE PROVE** | **CONSIDERAZIONI AGGIUNTIVE** |
|---|---|---|
| ○ Importante incertezza o variabilità<br>○ Possibile importante incertezza o variabilità<br>● Probabilmente nessuna incertezza o variabilità importante<br>○ Nessuna incertezza o variabilità importante | E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 4 record. Nessuno studio è stato incluso. | |

## 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<br>○ Probabilmente è in favore del confronto<br>○ Non è in favore né dell'intervento né del confronto<br>● Probabilmente è in favore dell'intervento<br>○ È in favore dell'intervento<br>○ Varia<br>○ Non lo so | Le prove sono limitate. | Esclusi pazienti TBI (in favore del confronto) in quanto in tale popolazione la rianimazione ipotensiva determina una riduzione della perfusione cerebrale con possibile danno secondario. |

## Risorse necessarie

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

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ Costi elevati<br>● Costi moderati<br>○ Costi e risparmi irrilevanti<br>○ Risparmi moderati<br>○ Risparmi elevati<br>○ Varia<br>○ Non so | E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 3 record: nessuno studio è stato incluso. Tuttavia, si inserisce la sezione dei costi unitari delle risorse necessarie riportate dalla linea guida NICE NG39 sulla gestione del trauma (NICE 2016).<br>**Unit costs (FROM NICE 2016) (tabella sottostante)**<br>La linea guida NICE (NICE 2016) riporta i costi unitari dei prodotti utilizzati nelle strategie di intervento (permissive hypotension vs normotension), di seguito la tabella: | |

| Resource | Cost | Source |
|---|---|---|
| Crystalloids:<br>• 0.9% Sodium Chloride (1000-ml bag)<br>• Hartmann's Solution (1000-ml bag)<br>• Plasmalyte M (1000-ml bag) Ringer's<br>• Lactate (500-ml bag) | <br>£0.70<br>£0.85<br>£0.91<br>£1.25 | IV fluid guideline |
| Packed red blood cells | £122 | NHS Blood and Transplant price list 2014/15 [105] |
| Fresh frozen plasma[a] | £28 | NHS Blood and Transplant price list 2014/15 |
| Platelets | £197 | NHS Blood and Transplant price list 2014/15 |
| Pooled cryoprecipitate (5 packs)[a] | £181 | NHS Blood and Transplant price list 2014/15 |

*(a) Can be considerably more expensive if the methylene blue versions of these products are used for children.*

Costi addizionali potrebbero essere necessari per la gestione e amministrazione del prodotto e possono variare a seconda del prodotto in uso.

**Contesto Italiano**

E' stata effettuata una ricerca su database e documentazione riportante capitolati di gara inerenti ad aziende ospedaliere ed aziende sanitarie locali per reperire i prezzi dei fluidi e dei materiali di consumo necessari alla loro somministrazione. Sono stati reperiti alcuni dati che dimostrano come In molti casi non sia possibile individuare dati coerenti con quelli mostrati dalla evidenza di letteratura poiché molte marche in Italia non sono in commercio. Inoltre i nomi commerciali delle soluzioni disponibili nel nostro Paese, sono diversi.
In generale i prezzi delle soluzioni saline reperite variano dai € 0,20 ai € 0,70, mentre la media dei prezzi in gara dei fluidi si attesta a 5,5 ogni 500 millilitri.
Anche per quanto riguarda i prezzi delle cannule è stata effettuata una ricerca nella documentazione relativa a i capitolati di gara delle aziende sanitarie e delle aziende ospedaliere italiane. Esistono molte tipologie di cannule ed il prezzo medio è risultato pari ad € 1,5 per ogni kit.
Vedi **Appendice G** per ulteriori dettagli.

## 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<br>● Bassa<br>○ Moderata<br>○ Alta<br>○ Nessuno studio incluso | Non ci sono giudizi inerenti la qualità delle prove essendo le prove relative alle risorse necessarie riportate dalla LG NG39 del NICE (NICE 2016) e contestualizzate in Inghilterra. Essendo il contesto inglese differente dal contesto italiano in termini di sistema sanitario nazionale, disponibilità di risorse economiche, la qualità delle prove potrebbe risentire di trasferibilità (indirectness), perciò con limitata applicabilità al contesto italiano. In particolare, non si evidenziano elementi che consentano di risalire alle unità fisiche di assorbimento delle risorse (cost drivers). | |

## Costo-efficacia

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

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ È in favore del confronto<br>○ Probabilmente è in favore del confronto<br>○ Non è in favore né del confronto né dell'intervento<br>● Probabilmente è in favore dell'intervento<br>○ È in favore dell'intervento<br>○ Varia<br>○ Nessuno studio incluso | È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 4 record relativi alla costo-efficacia della gestione delle emorragie nel trauma. E' stato incluso solo lo studio di Turner et al. (2000), che ha condotto una valutazione di costo-beneficio basato su un RCT.<br>Sebbene la qualità dello studio selezionato sia da considerarsi buona (75% sulla checklist CHEERS), mancano una serie di informazioni molto rilevanti: una proiezione dei risultati su una popolazione più ampia, una proiezione aldilà dell'orizzonte temporale del trial, ed in generale un'analisi probabilistica multivariata. Inoltre, i dati di assorbimento delle risorse sono riportati solo in parte. Infine, lo studio non riporta dati inerenti la qualità della vita, anche se le differenze nei parametri di efficacia sono pressoché nulle, rendendo quindi qualsiasi ulteriore analisi superflua.<br>Anche se la valutazione della generalizzabilità delle evidenze riportate, secondo apposita checklist validata a livello internazionale, restituisce come esito finale la specificità dei risultati relativamente al contesto di studio (britannico), le differenze nulle riguardo all'efficacia ed il basso costo dei fluidi, fanno propendere per una accettazione dei risultati come validi anche per il contesto italiano. Di conseguenza, dal punto di vista delle evidenze di costo efficacia, si può asserire che non esiste differenza fra la somministrazione di fluidi in pre-ospedalizzazione rispetto alla somministrazione in regime di ospedalizzazione. Per dettagli ulteriori si veda l'**Appendice G**. | |

## Equità

Quale sarebbe l'impatto in termini di equità?

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ Riduce l'equità<br>○ Probabilmente riduce l'equità | Non sono stati identificati studi relativi al contesto internazionale e italiano. | |

| | | |
|---|---|---|
| ○ Probabilmente nessun impatto<br>○ Probabilmente migliora l'equità<br>● Migliora l'equità<br>○ Varia<br>○ Non so | | |

## Accettabilità

L'intervento è accettabile per i principali stakeholders?

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ No<br>○ Probabilmente no<br>● Probabilmente sì<br>○ Si<br>○ Varia<br>○ Non so | È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 51 records relativi all'accettabilità/fattibilità della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero. Non ci sono studi rispondenti al quesito. | |

## Fattibilità

È fattibile l'implementazione dell'intervento?

| GIUDIZI | RICERCA DELLE PROVE | CONSIDERAZIONI AGGIUNTIVE |
|---|---|---|
| ○ No<br>○ Probabilmente no<br>● Probabilmente sì<br>○ Si<br>○ Varia<br>○ Non so | È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 51 records relativi all'accettabilità/fattibilità della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero. E' stato incluso uno studio randomizzato e controllato (Schreiber, Meier et al. 2015) pubblicato nel 2015 in USA per valutare la fattibilità e la sicurezza di una rianimazione controllata (CR) verso la rianimazione tradizionale nei pazienti con trauma e ipotesi in un setting pre-ospedaliero.<br>Sono stati arruolati 192 pazienti in setting pre-ospedaliero (coinvolte 19 EMS systems) con pressione sistolica ≤ 90 mmHg (pazienti nel gruppo CR hanno ricevuto 250 cc fluid se senza polso radiale o SBP < 70 mmHg e boli addizionali di 250 cc per mantenere polso radiale o SBP ≥ 70 mmHg).<br>Considerando gli outcomes: mortalità, ICU-free days, ventilator-free days, eventi avversi, lo studio pilota ha dimostrato che una strategia di rianimazione controllata può essere implementata con successo nel setting civile con una continuità di cura che inizia in fase pre ospedaliera e continua in fase ospedaliera sino al controllo definitivo dell'emorragia. | |

## RIASSUNTO DEI GIUDIZI

| | GIUDIZI | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEMA** | No | Probabilmente no | Probabilmente si | **Si** | | 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** | **N22. A favore del confronto** | Probabilmente a favore del confronto | Non è favorevole né al confronto né all'intervento | **N21. 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 si** | Si | | Varia | Non so |
| **FATTIBILITÀ** | No | Probabilmente no | **Probabilmente si** | Si | | Varia | Non so |

## Tipo di raccomandazione

### N. 21

| 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 (no TBI)** | Raccomandazione forte a favore dell'intervento |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

### N. 22

| **Raccomandazione forte contro l'intervento (TBI)** | 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 21. Nei pazienti con trauma ed instabilità emodinamica o shock e senza evidenza di trauma cranico si suggerisce una rianimazione volemica secondo una strategia di ipotensione permissiva (target PA sistolica 70 – 90 mmHg) fino al controllo definitivo dell'emorragia [Raccomandazione condizionata, qualità delle prove molto bassa].**

**Racc 22. Nei pazienti con trauma ed instabilità emodinamica o shock ed evidenza di trauma cranico moderato-severo non si raccomanda una rianimazione volemica secondo una strategia di ipotensione permissiva ma un'infusione di fluidi con un obiettivo di pressione arteriosa più elevata (target PA sistolica 100-110 mmHg) [Raccomandazione forte, qualità delle prove molto bassa].**

### Giustificazione

Le evidenze (anche se di bassa qualità) suggeriscono un beneficio in termini di sopravvivenza con la strategia ipotensiva controllata. Il controllo dell'emorragia deve essere il più tempestivo possibile per evitare ipotensioni prolungate capaci di determinare disfunzioni d'organo ed apparati.
L'apprezzabilità dei polsi centrali è indicativa di una PA sist di circa 70 mm Hg; il polso radiale è apprezzabile solitamente con una PA sistolica di almeno 90 mmHg.
Per i pazienti con TBI i rischi di una ipotensione permissiva eccedono i benefici attesi e questa strategia non è raccomandata sulla base del consenso degli esperti. Infatti, la perfusione cerebrale può essere già alterata da un aumento della pressione intracranica per cui un'ulteriore riduzione della PA sistemica potrebbe causare un danno cerebrale secondario aggiuntivo.

## Considerazioni relative ai sottogruppi

Vedi TBI sottogruppo.

## Considerazioni per l'implementazione

Nessuna.

## Monitoraggio e valutazione

L'impiego della strategia va monitorato per gli esiti conseguenti.

## Priorità della ricerca

Pazienti con TBI.

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## Appendice A - Quesito clinico e strategia di ricerca

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero.*

| **Review question: What are the most clinically and cost effective fluid resuscitation strategies in the major trauma patient (hypotensive vs. normotensive)?** | |
|---|---|
| Objective: To identify the optimal fluid resuscitation strategy for adults, young people and children | |
| Population | Children, young people and adults experiencing a traumatic incident with acute haemorrhage. |
| Intervention | 1. Combination of permissive hypotension and normotension<br>2. Permissive hypotension |
| Comparison | Resuscitation with normotension as aim |
| Outcomes | Critical:<br>Mortality at 24 hours, 30days/1 month, and 12 months<br>Health related quality of life<br>Neurological outcome<br>Length of intensive care stay<br>Blood product use<br><br>Important:<br>Multi organ failure<br>Time to definitive control of haemorrhage<br>Patient-reported outcomes: pain/discomfort return to normal activities psychological wellbeing<br><br>Population size and directness:<br>No limitations on sample size<br>Studies with indirect populations will not be considered. |
| Exclusion | People with a major trauma resulting from burns |
| Search strategy | Databases: Medline, Embase, the Cochrane Library<br>Date: All years updating NICE NG39<br>Language: Restrict to English only<br>Study designs: RCTs or Systematic reviews of RCTs; cohorts if no RCTs retrieved. |
| The review strategy | Quality of life data: Collect all data for the stated QoL measure, for metaanalysis and GRADE report only overall scores.<br>Appraisal of methodological quality: The methodological quality of each study will be assessed using AMSTAR 2 for SRs, risk of bias for RCTs and GRADE approach for certainty of evidence. |
| Analysis | Stratify by age: children (0-17 years), adults (18 and over)<br>Pre-hospital or hospital setting<br>Blunt or penetrating trauma<br><br>Sub-groups if between-study heterogeneity exists:<br>Co-existing traumatic brain injury |

| | |
|---|---|
| | Within-study confounders (if cohorts used)<br>Age<br>Injury severity<br>Depth of shock<br>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} |

### Haemorrhage population

## Medline search terms

| | |
|---|---|
| 1. | hemorrhage/ or exsanguination/ or shock/ or shock, hemorrhagic/ or shock, traumatic/ or Hypovolemia/ |
| 2. | (hypovol?em* or shock or exsanguin* or olig?em* or h?emorrhag* or hypoperfus*).ti,ab. |
| 3. | (coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti,ab. |
| 4. | (bleed* or bloodloss*).ti,ab. |
| 5. | (blood* adj3 loss*).ti,ab. |
| 6. | or/1-5 |

## Embase search terms

| | |
|---|---|
| 1. | exp *hypovolemia/ or *hemorrhagic shock/ or *traumatic shock/ or exp *bleeding/ or *exsanguination/ |
| 2. | (haemorrhag* or hemorrhag* or hypovol?em* or shock or exsanguin* or olig?em* or h?emorrhag* or hypoperfus*).ti,ab. |
| 3. | (coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti,ab. |
| 4. | (bleed* or bloodloss*).ti,ab. |
| 5. | (blood adj2 loss*).ti,ab. |
| 6. | or/1-6 |

## Cochrane search terms

| | |
|---|---|
| #1. | MeSH descriptor: [hemorrhage] this term only |
| #2. | MeSH descriptor: [exsanguination] this term only |
| #3. | MeSH descriptor: [shock] this term only |
| #4. | MeSH descriptor: [shock, traumatic] this term only |
| #5. | MeSH descriptor: [shock, hemorrhagic] this term only |
| #6. | MeSH descriptor: [hypovolemia] this term only |
| #7. | (haemorrhag* or hemorrhag* or hypovolem* or hypovolaem* or shock or exsanguin* or oligem* or oligaem* or hypoperfus*):ti,ab |
| #8. | (coagulopath* or (abnormal* near/2 coagulation) or hyperfibrinolysis):ti,ab |
| #9. | (bleed* or bloodloss*):ti,ab |
| #10. | blood* near/3 loss*:ti,ab |
| #11. | {or #1-#10} |

**INTERVENTION**

## Medline search terms

| | |
|---|---|
| 1. | fluid therapy/ |
| 2. | ((hypoten* or normoten* or euvol?emi* or normovol?emi* or hypovol?emi*) adj6 (permissive or resuscitat* or control*)).ti,ab. |
| 3. | ((fluid* or electrolyte*) adj6 (therap* or resuscitat* or administrat* or replace*)).ti,ab. |
| 4. | ((novel or hybrid) adj6 resuscitat*).ti,ab. |
| 5. | ((control* or restrict* or delay* or limit* or volume* or conserve or conservative) adj6 (iv or fluid* or electrolyte* or resuscitat* or intravenous*)).ti,ab. |
| 6. | rehydrat*.ti,ab. |
| 7. | (resuscitat* adj6 (plan* or strateg* or polic* or order* or decision* or protocol*)).ti,ab. |
| 8. | or/1-7 |

## Embase search terms

| | |
|---|---|
| 1. | fluid resuscitation/ |
| 2. | *fluid therapy/ |
| 3. | ((hypoten* or normoten* or euvol?emi* or normovol?emi* or hypovol?emi*) adj6 (permissive or resuscitat* or control*)).ti,ab. |
| 4. | ((Fluid* or electrolyte*) adj6 (therap* or resuscitat* or administrat* or replace*)).ti,ab. |
| 5. | ((novel or hybrid) adj6 resuscitat*).ti,ab. |

| | |
|---|---|
| 6. | ((control* or restrict* or delay* or limit* or volume* or conserve or conservative) adj6 (IV or fluid* or electrolyte* or resuscitat* or intravenous*)).ti,ab. |
| 7. | rehydrat*.ti,ab. |
| 8. | (resuscitat* adj6 (plan* or strateg* or polic* or order* or decision* or protocol*)).ti,ab. |
| 9. | or/1-8 |

## Cochrane search terms

| | |
|---|---|
| #1. | MeSH descriptor: [fluid therapy] this term only |
| #2. | ((hypoten* or normoten* or euvol?emi* or normovol?emi* or hypovol?emi*) near/6 (permissive or resuscitat* or control*)):ti,ab |
| #3. | ((fluid* or electrolyte*) near/6 (therap* or resuscitat* or administrat* or replace*)):ti,ab |
| #4. | ((novel or hybrid) near/6 resuscitat*):ti,ab |
| #5. | ((control* or restrict* or delay* or limit* or volume* or conserve or conservative) near/6 (iv or fluid* or electrolyte* or resuscitat* or intravenous*)):ti,ab |
| #6. | rehydrat*:ti,ab |
| #7. | (resuscitat* near/6 (plan* or strateg* or polic* or order* or decision* or protocol*)):ti,ab |
| #8. | {or #1-#7} |

## Appendice B - Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero.*

### Indice



### 1. Tabelle delle caratteristiche degli studi inclusi

| **Study** | **Albreiki 2017, Eur J Trauma Emerg Surg** |
|---|---|
| Study type | Systematic review |
| Number of studies/ number of participants | 5 trials and 5 observational studies<br>Overall, 4677 hypotensive patients with blunt or penetrating trauma. |
| Settings | Randomized and retrospective studies.<br>Studies conducted on humans and in clinical settings, either in pre-hospital or in-hospital critical care |
| Funding | None |
| Duration of study | Search up to May 2016 |
| Age, gender, ethnicity | The included studies were conducted on adult patients aged from 15 to 55 years, except three studies that examined the hypotensive resuscitation on a mixed population of elderly and non-elderly trauma patients. |
| Patient characteristics | Adult patients (aged ≥ 15 years) of blunt or penetrating trauma, with one or more documented episode of hypotension (systolic blood pressure ≤ 90 mmHg); |
| Intervention | Aggressive and restricted fluid resuscitation |
| Outcomes | - In-hospital mortality |

| **Study** | **Duan 2015, Int J Clin Exp Med** |
|---|---|
| Study type | Systematic review |
| Number of studies/ number of participants | 11 randomized controlled trials<br>Overall, 1482 subjects. |
| Countries and Settings | randomized or quasi-randomized<br>The study subjects were all human and clinical trials; no indication of clinical setting. |
| Funding | None |
| Duration of study | Up to january 2015 |
| Age, gender, ethnicity | Not reported |
| Patient characteristics | Mean arterial blood pressure (MAP) of patients in LFR group were all under 70 mmHg; MAP of hemorrhagic shock patients in RFR group were 80~90 mmHg |
| Intervention | 725 hemorrhagic shock patients who required emergent surgery selected limited fluid resuscitation (LFR)<br>757 patients underwent regular fluid resuscitation (RFR) during active hemorrhagic shock. |
| Outcomes | - mortality<br>- blood routine index (hemoglobin, Hb; Platelets, PLT; Hematocrit, Hct)<br>- blood coagulation function (Prothrombin Time, PT; activated partial thromboplastin time, APTT)<br>- blood gas analysis (base excess, BE; blood lactic acid, BLA)<br>- postoperative complications (such as MODS (multiple organ dysfunction syndrome) and ARDS (Acute Respiratory Distress Syndrome)) |

| **Study** | **Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine** |
|---|---|
| Study type | Systematic review |
| Number of studies/ number of participants | 20 trials, 4 observational studies<br>Overall, 2955 patients |
| Countries and Settings | Randomized controlled trials (RCTs) and cohort studies<br>Mixed setting: pre-hospital and in-hospital |
| Funding | None |
| Duration of study | Search up to January 2018 |
| Age, gender, ethnicity | Adult patients aged older than 18 years |
| Patient characteristics | Adult patients aged older than 18 years who had traumatic hemorrhagic shock and a systolic blood pressure below 90mmHg. |
| Intervention | Conventional fluid resuscitation with normotension (liberal fluid resuscitation) versus hypotensive resuscitation (limited fluid resuscitation). |
| Outcomes | - All-cause mortality,<br>- Complications: acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and multiple organ dysfunction (MODS).<br>- Fluid resuscitation volume<br>- Transfusion of packed red cells. |

| **Study** | **Safiejko 2020,Cardiology Journal** |
|---|---|
| Study type | Systematic review |
| Number of studies/ number of participants | 28 trials<br>Overall, 4503 patients |
| Countries and Settings | Randomized controlled trials (RCTs) and quasi-randomized trials.<br>Mixed setting: pre hospital and in hospital |
| Funding | Supported by the ERC Research Net and by the Polish Society of Disaster Medicine |
| Duration of study | Search up to June 2020 |
| Age, gender, ethnicity | Adult, age not specified |
| Patient characteristics | Traumatic hemorrhagic shock patients |
| Intervention | Hypotension fluid resuscitation versus conventional fluid resuscitation |
| Outcomes | - Mortality,<br>- Adverse events,<br>- Fluid balance and transfusion requirements,<br>- ICU and hospital lenght of stay |

| **Study** | **Tran 2018,Journal of Trauma and Acute Care Surgery** |
|---|---|
| Study type | Systematic review |
| Number of studies/ number of participants | 5 trials<br>Overall, 1158 patients |
| Countries and Settings | Randomized controlled trials and quasi-randomized trials<br>Mixed: pre hospital and in hospital |
| Funding | None |
| Duration of study | Search up to May 2017 |
| Age, gender, ethnicity | Adult, age not specified |
| Patient characteristics | Adult patients with penetrating or blunt traumatic injury and suspicion of hemorrhage. Civilian or military patient populations were both eligible. |
| Intervention | Permissive hypotension resuscitation versus conventional resuscitation |
| Outcomes | - 30-day or in-hospital mortality<br>- blood product utilization<br>- estimated blood loss<br>- in-hospital complications. |

## 2. Lista degli studi esclusi con motivazione

| | Study | Reason |
|---|---|---|
| 1 | Zhang. Clinical effects of two types of fluid infusion in pre-hospital care for traumatic shock. Biomedical research (india) 29, 1232-1235 (2018). | Wrong intervention |
| 3 | Avery, P., https://orcid.org, I.O., Avery, P., et al. Whole blood transfusion versus component therapy in adult trauma patients with acute major haemorrhage. Emergency medicine journal : EMJ 37, 370-378. | Wrong intervention |
| 4 | Carrick Matthew, M., Leonard, J., Slone Denetta, S., Mains Charles, W., Bar-Or, D. & https://orcid.org/---314X, I.O. Hypotensive Resuscitation among Trauma Patients. BioMed research international 2016, 8901938 (2016). | Narrative review |
| 6 | de Crescenzo, C., Gorouhi, F., Salcedo Edgardo, S. & Galante Joseph, M. Prehospital hypertonic fluid resuscitation for trauma patients: A systematic review and meta - analysis. The journal of trauma and acute care surgery 82, 956-962. | Wrong intervention |
| 8 | Duchesne Juan, C., Kaplan Lewis, J., Balogh Zsolt, J. & Malbrain Manu, L.N.G. Role of permissive hypotension , hypertonic resuscitation and the global increased permeability syndrome in patients with severe hemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension. Anaesthesiology intensive therapy 47, 143-155 (2015). | Narrative review |
| 11 | Safiejko, K., Szarpak, L., Smereka, J., et al. Efficacy and safety of hypertonic saline solutions fluid resuscitation on hypovolemic shock : A systematic review and meta - analysis of randomized controlled trials. Cardiology journal 3, 1897-5593 (2020). | duplicate |
| 13 | Schreiber, M.A.D., McCully, B.H., Newgard, C.D., et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: Results of a prospective randomized pilot trial. Journal of Trauma and Acute Care Surgery 78, 687-697. | duplicate |
| 14 | Shao, Z., Du, Z., Wang, R., et al. Effects of different target blood pressure resuscitation on peripheral blood inflammatory factors and hemodynamics in patients with traumatic hemorrhagic shock. Zhonghua wei zhong bing ji jiu yi xue 31, 428-433 (2019). | Awaiting assessment |
| 16 | Wang, H., Chen, M.-B., Zheng, X.-W. & Zheng, Q.-H. Effectiveness and safety of hypotensive resuscitation in traumatic hemorrhagic shock : A protocol for meta - analysis. Medicine 98, e18145. | protocol of SR |
| 17 | Yu, J.-Y.D., Peng, J.-H., Hui, L., Huang, H.-Q., Tan, M.-H. & Jian, G. Association between the effect of controlled fluid resuscitation on massive hemorrhage and expression of human neutrophil lipocalin. Experimental and Therapeutic Medicine 16, 3534-3538. | Wrong outcome |

## 3. Overlapping of PICOs

| | ALBREIKI 2017 | DUAN 2015 | OWATTANAPANICH 2018 | SAFIEJKO 2020 | TRAN 2018 |
|---|---|---|---|---|---|
| **NUMBER OF STUDIES** | 5 RCTs and 5 observational studies, up to may 2016 | 11 RCTs, up to january 2015 | 20 RCTs, 4 observational studies up to january 2018 | 28 RCTs or quasi - RCTs*, up to june 2020 | 5 RCTs, up to may 2017 |
| **POPULATION** | adult patients (aged ≥ 15 years) of blunt or penetrating trauma, with one or more documented episode of hypotension (systolic blood pressure ≤ 90 mmHg); | The trauma patients in the study presented with a common clinical syndrome - hemorrhagic shock | adult patients aged older than 18 years who had traumatic hemorrhagic shock and a systolic blood pressure below 90mmHg. | traumatic hemorrhagic shock patients | adult patients with penetrating or blunt traumatic injury and suspicion of hemorrhage. Civilian or military patient populations were both eligible. |
| **INTERVENTIONS** | normotensive and hypotensive trauma | fluid resuscitation | conventional fluid resuscitation with normotension (liberal fluid resuscitation) versus hypotensive resuscitation (limited fluid resuscitation). | hypotension versus conventional fluid resuscitation | permissive hypotension vs. conventional resuscitation |
| **LANGUAGES** | english | no language restriction | no language restriction | english | no language or date restrictions |
| **SETTING (DECLARED IN INCLUSION CRITERIA)** | Mixed (pre-hospital or in-hospital critical care) | No identification of clinical setting | Mixed (pre-hospital or in-hospital critical care) | Mixed (pre-hospital or in-hospital critical care) | Mixed (pre-hospital or in-hospital critical care) |
| **STUDY DESIGN** | randomized and retrospective studies | randomized or quasi-randomized | randomized controlled trials (RCTs) and cohort studies | randomized controlled trials (RCTs) and quasi-randomized trials. | randomized controlled trials and quasi-randomized trials |
| **EXCLUSION CRITERIA** | traumatic brain injury (TBI) | traumatic brain injury (TBI) | pregnant or traumatic brain injuries (TBI ) | not reported | traumatic brain injury (TBI) |

*Quasi-RCT is defined by SR'authors, however some studies are defines as comparative cohort (observational) in other SRs

## 4. Overlapping of included studies (randomized controlled trials and observational studies)

| | Albreiki 2017 | Duan 2015 | Owattanapanich 2018 | Safiejko 2020 | Tran 2018 |
|---|---|---|---|---|---|
| Bickell **et al. N Engl J Med.** 1994 | | | | | |
| Carrick **et al.J Trauma Acute Care Surg.** 2016 | | | | | |
| Chen Mianzhan **et al., China Academic Journal**. 2015 | | | | | |
| Chen Mu-hu et al, **Sichuan Medical Journal.** 2013 | | | | | |
| Chen Yuan-bing **et al.,Hunan Normal Univ.** 2015 | | | | | |
| Dai Yolong **et al. J Liaoning Medical University.**2016 | | | | | |
| Dutton **et al.J Trauma Acute Care Surg. 2002** | | | | | |
| Fan Hai-peng **et al. J Trauma Surg 2011** | | | | | |
| Fan hai-peng **et al., Clin J Med Offic. 2012** | | | | | |
| Haung Ting **et al, China Modern Doctor.** 2015 | | | | | |
| He **et al,Journal of Internal Intensive Medicine** 2012 | | | | | |
| Hua li-dain **et al ,Progress in Modern Biomedicine.** 2010 | | | | | |
| Li WH **et al.,Journal of Clinical Medical Engineering/ China Academic Journal.** 2012 | | | | | |
| Lu **et al, Journal of Qinghai Medical College** 2006 | | | | | |
| Lu **et al. Cell Biochem Biophys** 2015 **[Epub ahead of print].** | | | | | |
| Morrison **et al. J Trauma Acute Care Surg.** 2011 | | | | | |
| Schreiber **et al.J Trauma Acute Care Surg.** 2015**;** | | | | | |
| Tang **et al. Modern Practical Medicine** 2013**;** | | | | | |
| Turner **et al, Health Technology Assessment.** 2000 | | | | | |
| Wang Aitian**, et al, Tianjin Med J.** 2010 | | | | | |
| Wang **et al. J Medi Coll PLA**. 2007 | | | | | |
| Wang e**t al.J Hepatobiliary Surg**. 2014 | | | | | |
| Wang Fengyong **et al, Henan Meidcal Research** 2016 | | | | | |
| Wei **et al.,Journal of Youjiang National Medical College** 2008 | | | | | |
| Wen **et al.China Prac Med.** 2015; | | | | | |
| XU Grouping **et al, Chinese Journal of Disaster Medicine** 2015 | | | | | |
| YAO Jian-hui **et al, Chinese Journal of Frontier Medicine.**2015 | | | | | |
| ZENG Fan-yuan **et al, J Chin Pract Diagn Ther.** 2014**;** | | | | | |
| Zhao et al, **Medical Innovation of China.** 2013 | | | | | |
| Zheng Weihua **et al,Resuscitation and Disaster Medicine** 2007 | | | | | |
| Brown et al. **Trauma Acute Care Surg. 2013** | | | | | |
| Geeraedts et al.**Injury 2015** | | | | | |
| Kasotakis et al.**Trauma Acute Care Surg. 2013** | | | | | |
| Ley et al. **J Trauma Acute Care Surg. 2011** | | | | | |
| Talving et al.Prehosp Disaster Med. 2005; | | | | | |

## 5. Caratteristiche degli studi primari inclusi nelle 5 revisioni sistematiche incluse

| Author name, year | Hypotensive subjects (N) | Age range (mean) years | Study design | Site | Location | Population | Intervention | Control | SBP (mmHg) | ISS | PDF available |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bickell et al. N Engl J Med. 1994** | 598 | 20-20 (31) years | randomized | Pre-hospital | USA | penetrating trauma, SBP < 90 mmHg | Delayed resuscitation with RLS 10ml/hr until definitive treatment | immediate resuscitation to mantein SBP at least 100 mmHg | 75.5 | 26 | yes |
| **Brown et al. Trauma Acute Care Surg. 2013** | 616 | 19-89(40) | prospective (comparative) | Pre-hospital | USA | Blunt injury adults | with PH hypotension (systolic blood pressure [SBP], <90 mm Hg | without PH hypotension (systolic blood pressure [SBP], <90 mm Hg | 68 | 41 | NO |
| **Carrick et al.J Trauma Acute Care Surg. 2016** | 180 | 15-45(30) | randomized | Operating room | USA | trauma patients with an uncontrolled source of bleeding | Experimental Arm MAP ≥ 50 mm Hg | Control Arm MAP ≥ 65 mm Hg | 82 | 17.5 | yes |
| **Chen Mianzhan et al., China Academic Journal. 2015** | na | na | randomized | Na | China | traumatic hemorrhagic shock patients | limited resucitation (SBP at least 80 mmHg) | Conventional resuscitation (SBP at least 90 mmHg) | na | na | NO |
| **Chen Mu-hu et al, Sichuan Medical Journal. 2013** | na | na | randomized | Na | China | traumatic hemorrhagic shock patients | limited fluid resuscitation (SBP 70 mmHg) | aggressive fluid resuscitation (SBP 90 mmHg) | na | na | NO |
| **Chen Yuan-bing et al.,Hunan Normal Univ. 2015** | na | na | randomized | ED | China | traumatic hemorrahagic shock | limited resuscitation SBP 70 mmHg | Conventional resuscitation SBP>90 mmHg | na | na | NO |
| **Dai Yolong et al. J Liaoning Medical University.2016** | na | na | randomized | na | China | patients with severe closed traumatic hemorrhagic shock | limited resucitation | na | na | na | NO |
| **Dutton et al.J Trauma Acute Care Surg. 2002** | 110 | 17-42(31) | randomized | ED | USA | blunt and penetrating trauma | Low SBP of 70 mmHg | Conventional SBP > 100 mmHg | 107 | 21.73 | yes |
| **Fan Hai-peng et al. J Trauma Surg 2011** | 85 | na | randomized | ED | China | pelvic fracture with hemorrhagic shock | limited fluid resuscitation (SBP maintained with 70-90mmHg,MAP maintained with 50-60mmHg) | General fluid resuscitation | na | na | yes |
| **Fan hai-peng et al., Clin J Med** | na | na | randomized | na | China | hepatic and splenic injury | limited fluid resuscitation (MAP | conventional resuscitation | na | na | NO |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Offic. 2012** | | | | | | with hemorragic shock | 50-60 mmHg) | (SBP 100 mmHg or MAP 60-80 mmHg) | | | |
| **Geeraedts et al.Injury 2015** | 941 | ≥16 years | retrospective (non-comparative) | Pre-hospital | Australia | Blunt trauma (79%) and penetrating trauma | Fluid resuscitation | na | 81 | 13 | NO |
| **Haung Ting et al, China Modern Doctor. 2015** | na | na | randomized | na | China | tramatic hemorrhagic shock | control group with MAP 40-60 mmHg | Observation group with MAP 60-90 mmHg | na | na | NO |
| **He et al,Journal of Internal Intensive Medicine 2012** | na | na | randomized | na | China | hemorrhagic shock caused by acute upper gastrointestinal hemorrhage | limited fluid resuscitation | na | na | na | NO |
| **Hua li-dain et al ,Progress in Modern Biomedicine. 2010** | na | na | randomized | na | China | severe multiple hemorrhagic shock | limited fluid resuscitation (SBP 70 mmHg) | observational with MAP at least 90/60 mmHg | na | na | NO |
| **Kasotakis et al.Trauma Acute Care Surg. 2013** | 1754 | 16-90 (43.5) | prospective (non-comparative) | in-hospital | USA | adult blunt trauma patients | aggressive early crystalloid resuscitation | na | 111.1 | 32.2 | NO |
| **Ley et al. J Trauma Acute Care Surg. 2011** | Overall: 3137; Hypotens 106 | 20-69(37) | retrospective (non-comparative) | ED | USA | Trauma patients | crystalloid fluid resuscitation | na | 133 | 10.3 | NO |
| **Li WH et al.,Journal of Clinical Medical Engineering/ China Academic Journal. 2012** | na | na | randomized | na | China | traumatic hemorragic shock without controlling bleeding | limited fluid resuscitation (MAP 55 mmHg) | adequate fluid resuscitation (MAP 75 mmHg) | na | na | NO |
| **Lu et al, Journal of Qinghai Medical College 2006** | na | na | randomized | na | China | abdomen hemorrhagic shock | early restriction resuscitation treatment | na | na | na | non c'è in safajieko |
| **Lu et al. Cell Biochem Biophys 2015 [Epub ahead of print].** | 51 | 26-63 | randomized | In hospital | China | acute upper gastrointestinal bleeding due to liver cirrhosis and concomitant hemorrhagic shock | limited fluid resuscitation (SBP 80-90 mmHg) | traditional fluid resuscitation regimen (SBP ≥90 mmHg) | na | Not trauma | SI |
| **Morrison et al. J Trauma Acute Care Surg. 2011** | 90 | 15-45(32.3) | randomized | Operating room | USA | blunt and penetrating trauma | mantein MAP > 50 mmHg | Mantein MAP > 65 mmHg | 75.85 | 19.1 | SI |
| **Schreiber et al.J Trauma Acute Care Surg. 2015;** | 192 | ≥ 15 years(41) | randomized | Pre-hospital | USA/Canada | blunt or penetrating truama patients | Administer 250 ml of fluid if SBP <70 | Administer 2 liters initially and | 82.7 | 32.5 | SI |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | with SBP <90 | | additionally fluis asneedeed to maintain SBP > 100 mmHg | | | |
| **Talving et al.Prehosp Disaster Med. 2005;** | 102 | 22-55(35.5) | retrospective (non-comparative) | Pre-hospital | Europe (Sweden) | Penetrating (25%) and blunt trauma hypotensive patients (systolic blood pressure «s90 mmHg on the scene of injury) | Fluid resuscitation | na | U/S | 28.5 | no |
| **Tang et al. Modern Practical Medicine 2013;** | na | na | randomized | na | na | esophageal variceal bleeding combined with hemorrhagic shock | limited fluid resuscitation | na | na | na | no |
| **Turner et al, Health Technology Assessment. 2000** | 1309 | > 16 years | randomized | Pre-hospital | Europe (United Kingdom) | blunt and penetrating trauma | intravenous fluids were administered at the incident scene to all adult trauma patients who under current procedures the paramedic would consider starting on intravenous fluids. | fluids were withheld until arrival at hospital, unless the time to hospital was likely to be over 1 hour. | na | na | SI |
| **Wang Aitian, et al, Tianjin Med J. 2010** | | na | randomized | na | China | traumatic hemorrhagic shock | limited fluid resuscitation to mantein SBP 70 mmHg | conventional resuscitaiton to mantein SBP 100 mmHg | na | na | no |
| **Wang et al. J Medi Coll PLA. 2007** | | na | prospective chort study | na | China | traumatic hemorrhagic shock | preoperative SBP approximately 70-80 mmHg | preoperative SBP > 90 mmHg | na | na | SI |
| **Wang et al.J Hepatobiliary Surg. 2014** | | na | randomized | na | China | traumatic liver and splenic injury | Limited fluid resuscitation (MAP 50-70 mmHg) | Conventional resuscitation (MAP 70-90 mmHg) | na | na | no |
| **Wang Fengyong et al, Henan Meidcal Research 2016** | | na | randomized | na | China | patients with active hemorrhagic shock | limited fluid resuscitation | na | na | na | NO |
| **Wei et al.,Journal of Youjiang National Medical College 2008** | 56 | na | randomized | na | China | hemorrhagic patients | Limited fluid resuscitation | na | na | na | NO |
| **Wen et al.China Prac Med. 2015;** | | na | prospective chort | na | China | traumatic hemorrhagic | limited fluid resuscitation(SBP 75 | Conventional fluid | na | na | no |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | shock | mmHg) | resuscitation (SBP>100 mmHg) | | | |
| **XU Grouping et al, Chinese Journal of Disaster Medicine 2015** | | na | randomized | na | China | traumatic hemorrhagic shock | limited fluid resuscitation(MAP 40-60 mmHg or SBP 70 mmHg) | Conventional fluid resuscitation (MPA 60-80 mmHg oe SBP>90 mmHg) | na | na | no |
| **YAO Jian-hui et al, Chinese Journal of Frontier Medicine.2015** | | na | randomized | na | China | multiple trauma and hemorrhagic shock | limited fluid resuscitation | active fluid resuscitation | na | na | no |
| **ZENG Fan-yuan et al, J Chin Pract Diagn Ther. 2014;** | | na | cohort study | na | China | uncontrolled traumatic hemorrhagic shock | experimental group (MAP 50 mmHg) | Control group (MAP 70 mmHg) | na | na | no |
| **Zhao et al, Medical Innovation of China. 2013** | | na | retrospective cohort study | na | China | traumatic hemorrhagic shock patients | Objective group (SBP 85 mmHg, limited fluid) | Control group (SBP > 90 mmHg, rapid and full replenishment of fluid) | na | na | no |
| **Zheng Weihua et al,Resuscitation and Disaster Medicine 2007** | | na | randomized | na | China | traumatic hemorrhagic shock patients | limited fluid resuscitation (MAP 50-60 mmHg) | Aggressive fluid resuscitation (MAP 70 mmHg) | na | na | No |

## Appendice C. Sintesi delle evidenze

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero.*

# INDICE

## INCLUSION CRITERIA

According to the PICOS method (Greenhalgh 1997, O'Connor 2008, Richardson 1995) we followed the hierarchy for study designs according to the effectiveness questions on which firstly SRs and then randomised controlled trials are considered as the best source of evidence. Thus, if no systematic reviews was found, a search of primary studies was performed.

**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 according to the following criteria:

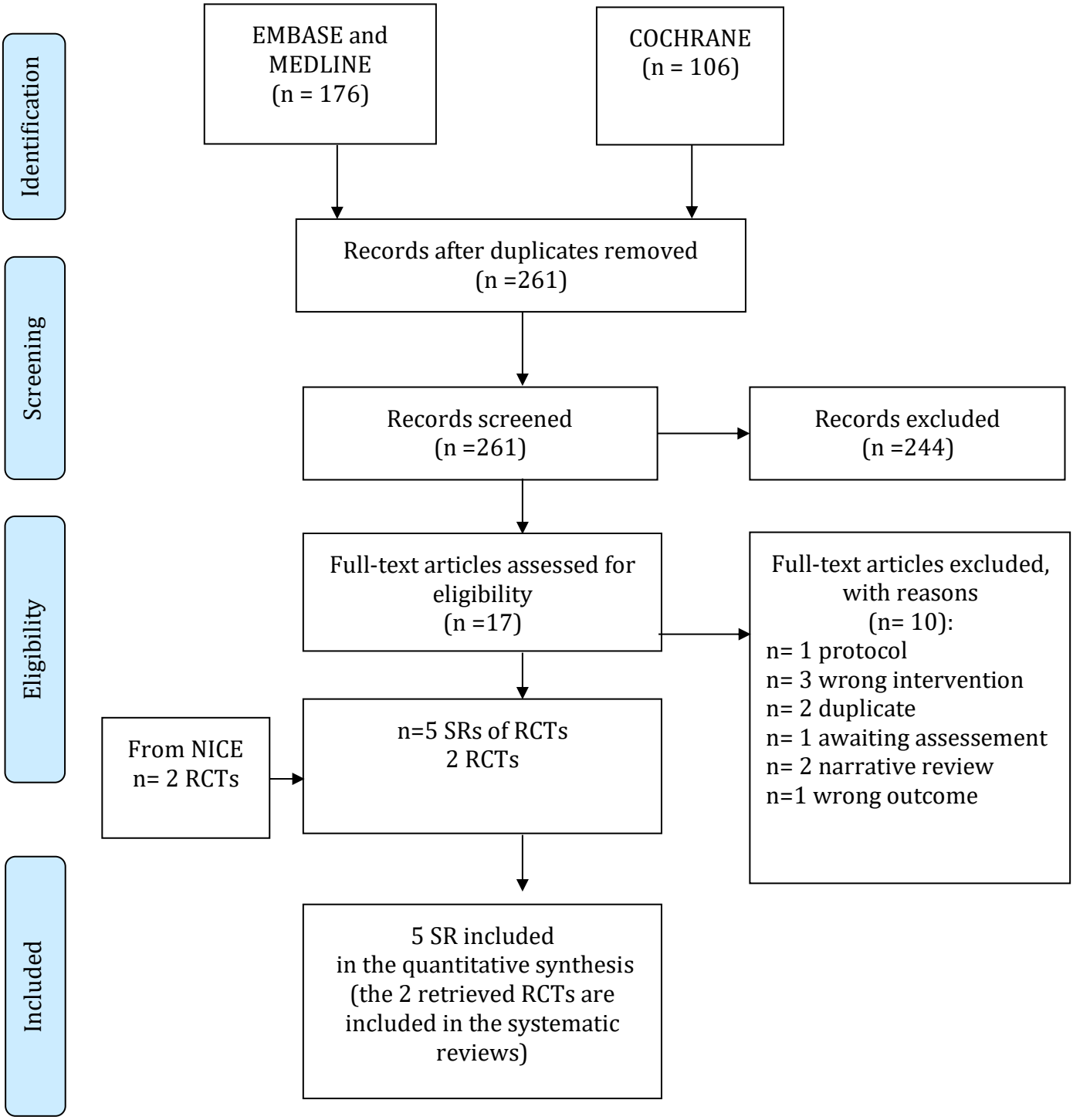
1. the methodological quality of the review ( assessed by AMSTAR 2);
2. the update of the bibliographic search;
3. the level of overlapping of included primary studies and outcomes;
4. the quality of evidence coming from the included studies;

However, in case of similar methodological quality of the review, update search, quality of evidence, presence of all eligible studies, and different outcomes addressed in several SRs, we transparently presented all the evidence coming from the eligible SRs according to the overview of review methodology (1) trying to cover of all outcomes planned for showing the desirable and undesirable effects, (2) presenting outcome data exactly as they appear in the included systematic reviews, without a re-analysis of the outcome data conducted in the systematic reviews.

**Primary studies (RCTs or observational studies)**: we followed a hierarchy of the study designs according to the effectiveness questions on which randomised controlled trials are considered as the best source of evidence in absence of systematic reviews.

SELEZIONE DEGLI STUDI

**Figure 1. Flow Chart of study selection**



## OUTCOME ASSESSMENT

E' stata effettutata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono state individuate 5 SRs e 2 trials che soddisfano i criteri per rispondere al quesito clinico proposto.
Osservando il confronto tra le RS, gli studi randomizzati e controllati identificati dalla strategia di ricerca ed estrapolati dalla linea guida NICE sono inclusi nelle RS selezionate; inoltre, valutando l'overlapping del PICO delle revisioni incluse, questi sono sovrapponibili.
Le RS presentano outcomes e qualità metodologica simili, valutata tramite l'AMSTAR 2 (vedi appendice D).
Adottando la metodologia delle overview of reviews (1), riportiamo descrittivamente i risultati degli outcome riportati dalle revisioni incluse. Laddove la qualità delle evidenze valutata con la metodologia GRADE non è riportata per ogni outcome nelle revisioni sistematiche, il giudizio verrà calcolato e assegnato dall'evidence review team della presente linea guida utilizzando le informazioni disponibili delle revisioni in oggetto e applicando i singoli domini (risk of bias, indirectness, inconsistency, imprecision and publication bias) previsti dalla metodologia GRADE.
Le revisioni incluse permettono di rispondere alle seguente comparazione:

- hypotensive fuid resuscitation versus conventional fluid resuscitation

Gli outcome riportati tra le reviews sono riportati in tabella:

| | **Outcomes** | **Albreiki 2017** | **Duan 2015** | **Owattanapanich 2018** | **Safiejko 2020** | **Tran 2018** |
|---|---|---|---|---|---|---|
| Critical | Mortalità | | | | | |
| Critical | Health relatred-quality of life | | | | | |
| Critical | Neurological outcomes | | | | | |
| Critical | Durata del ricovero in terapia intensiva | | | | | |
| Critical | Necessità di trasfuzioni | | Platelets | PRBC | Platelets,PRBC Fresh frozen plasma | Descrittive generali |
| Important | Multiple organ dysfunction syndrome | | | | | |
| Important | Time to definitive control of hemmorage (hours) | | Prothrombin time; activated partial thromboplastin time | | | Time to hemostatis (hours) |
| Important | Patient reported outcomes | | | | | |

## *CRITICAL OUTCOMES*

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

Tutte le revisioni incluse riportano l'outcome di interesse. Nello specifico Duan 2015, Owattanapanich 2018, Safiejko 2020 e Tran 2018 (2-5) riportano dati quantitativi sulla mortalità senza specificare follow-up mentre Albreiki 2017 (6) riporta dati sia in termini di mortalità che di sopravvivenza come frequenze cumulate ma senza riportare una stima complessiva quantitativa fra gli studi.
Di seguito si riportano i dati di mortalità per ciascuna revisione sistematica.

**Albreiki 2017**
The included RCTs showed that the mortality rate in 1157 trauma patients resuscitated with low and large volumes of fluid was 21.5% (123 deaths from 570 patients) and 28.6% (168 deaths from 587 patients), respectively.
The collective comparative studies that encompassed five RCTs and one prospective study (Brown et al.) showed that the pooled survival rate of limited versus liberal volume resuscitation was 82.9 and 80.2%, respectively.

**Table 4** Pooled mortality rate between hypotensive and aggressive resuscitation groups in the comparative studies

| Name, year | Sample size of hypotensive patients | No of deaths | | *P* value | Hazard ratio | Survival rate between restrictive versus large volume resuscitation (%) |
|---|---|---|---|---|---|---|
| | | Death/patients (hypotensive group) (%) | Death/patients (aggressive group) (%) | | | |
| Randomised control trials and prospective study | | | | | | |
| Bickell et al. [13] | 598 | 86/289 (29.7) | 116/309 (37.5) | 0.04 | N/M | 70 versus 62 |
| Dutton et al. [26] | 110 | 4/55 (7.2) | 4/55 (7.2) | N/M | HR 1.00 | 92.7 versus 92.7 |
| Morrison et al. [27] | 90 | 10/44 (22.7) | 13/46 (28.2) | 0.58 | HR 1.10 | 77.2 versus 71.7 |
| Schreiber et al. [28] | 191 | 5/96 (5.2) | 14/95 (14.7) | N/M | aOR 0.39 | 94.8 versus 85.2 |
| Carrick et al. [29] | 168 | 18/86 (20.9) | 21/82 (25.6) | 0.47 | HR 0.48 | 78.5 versus 73.7 |
| Total | 1157 | 123/570 (21.57%) | 168/587 (28.6%) | | | |
| Prospective cohort study | | | | | | |
| Brown et al. [31] | 603 | 19/123 (15.4%) | 18/480 (3.75) | 0.90 | HR 0.81 | 84.55 versus 96.25 |

| Groups | Population (*n*) | Mortality *n* (%) | Survival rate (mean) |
|---|---|---|---|
| Calculation of overall mortality rate and survival rate | | | |
| Hypotensive resuscitation | 693 | 142 (20.49) | 82.95% |
| Aggressive resuscitation | 1067 | 186 (17.43) | 80.25% |

*aOR* adjusted odds ratio, *n* number, *vs.* versus

**Duan 2015**
Nine studies including 1,384 patients compared the mortality of hemorrhagic shock patients between limited fluid resuscitation (LFR) and regular fluid resuscitation (RFR). The heterogeneity test indicated that there was little heterogeneity between LFR and RFR groups ($\chi 2 = 12.35$; $P = 0.14$; $I2 = 35\%$) and fixed model was used. In these trials, mortality for LFR group vs. RFR group was 131 of 675 (19.4%) vs. 208 of 709 (29.3%). The results indicated that limited fluid resuscitation may reduce the mortality in patients with hemorrhagic shock (RR = 0.67; 95% CI = 0.56-0.81; $P < 0.0001$) (Figure 2). In order to investigate whether human species influence the mortality of hemorrhagic shock after LFR or RFR, we did subgroup analysis to 3 trials from America and 6 trials from China, respectively. The consequences of subgroup analysis were consistent with the total analysis. However, the difference of mortality between LFR and RFR groups in America descent was not significant as that in Asian descent.

**Owattanapanich 2018**

A pooled analysis was performed of the 24 studies using a random-effects model, with findings reported as RR and 95% CI (n = 1473; RR: 0.50; 95% CI: 0.40– 0.61). A mild heterogeneity among these 24 studies was observed (Q test: 0.11, which is greater than 0.1; I2: 27%). Given the degree of homogeneity among the studies, a random-effects model was subsequently applied (Fig. 4). As described in Fig. 4, some overtime bias was observed among the studies. Although the first published study on this topic (by Bickell WH et al. [2]) was published in 1994, we still included it due to its sound methodology and overall high level of quality.

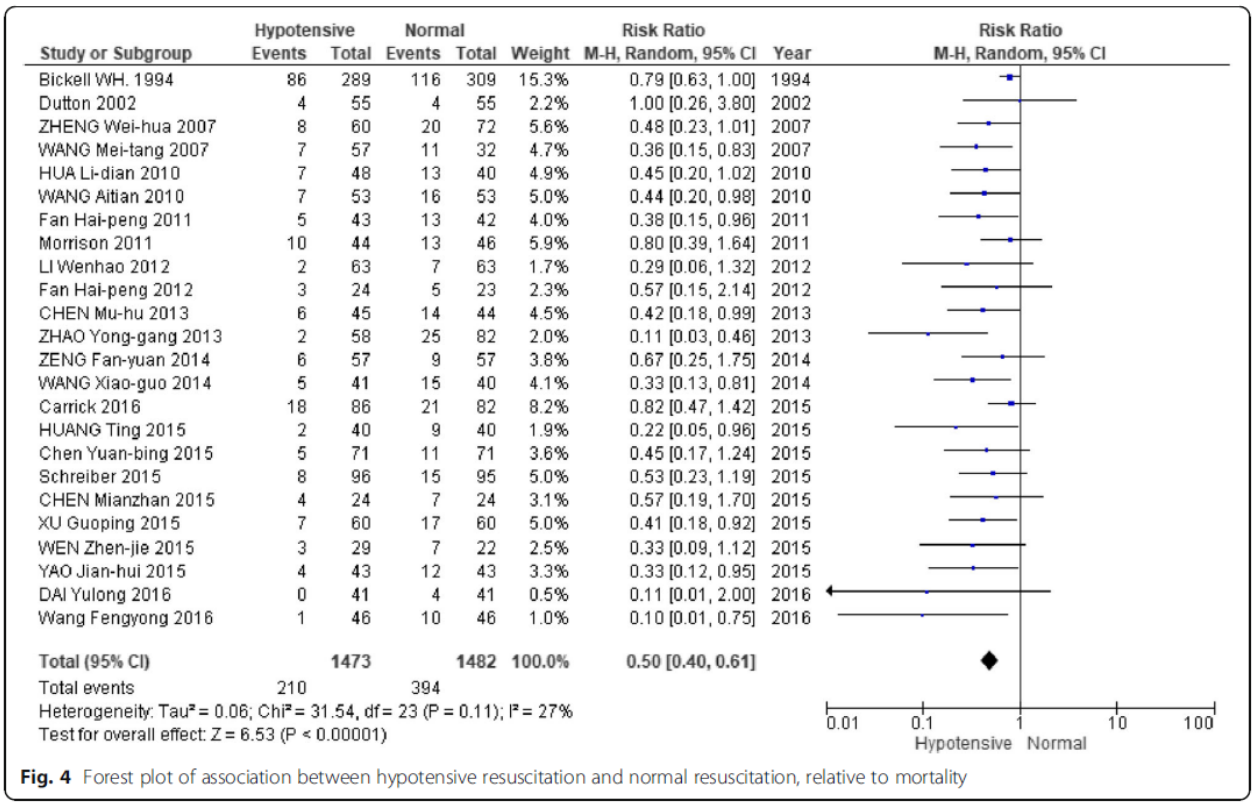



**Fig. 4** Forest plot of association between hypotensive resuscitation and normal resuscitation, relative to mortality

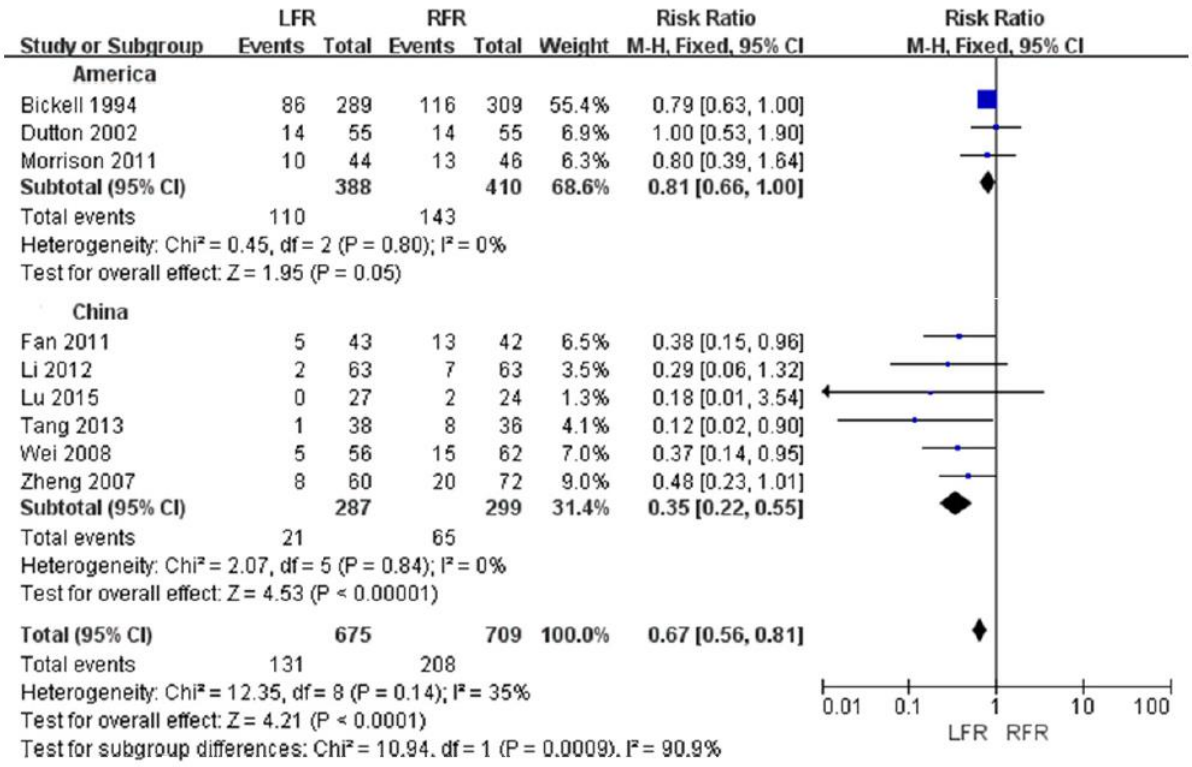



**Figure 2.** Forest plot illustrating the mortality between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; M-H, Mantel-Haenszel.

**Safajeiko 2020**

Twenty-eight studies reported overall mortality [16–23]. Mortality with hypotension fluid resuscitation was 12.5% and was statistically significant, being smaller than with the conventional fluid resuscitation group – 21.4% (RR = 0.58; 95% CI: 0.51–0.66; I2 = 37%; p < 0.001; Fig. 2). In contrast, only one study by Morrison et al. [28] indicated mortality rates during the first 24 hours. According to this study, mortality for hypotension versus conventional fluid resuscitation varied and amounted to 13.6% vs. 21.7% respectively (RR = 0.63; 95% CI: 0.25–1.58; p = 0.32).

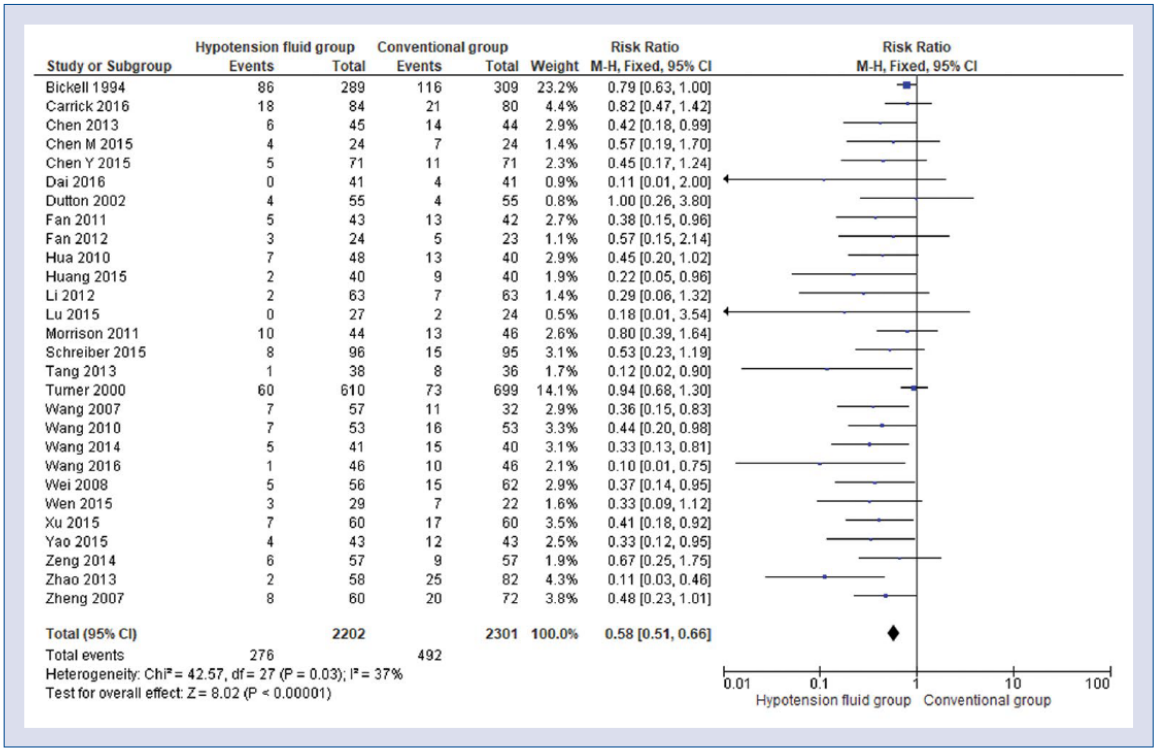
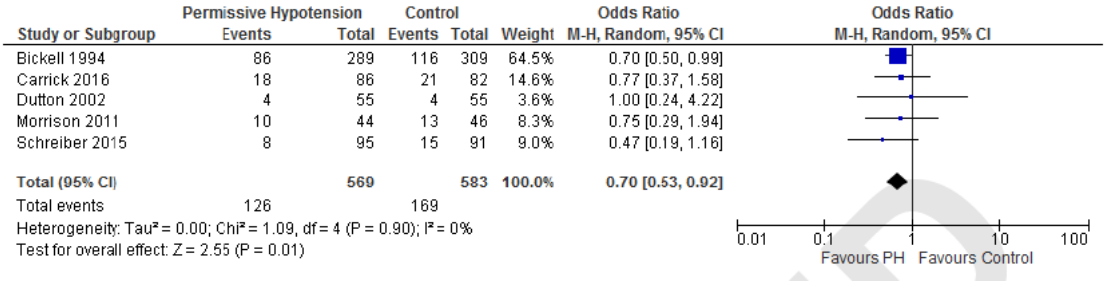



**Figure 2.** Forest plot of hypotension versus. conventional fluid resuscitation, relative to mortality. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

## Tran 2018

Two studies presented 30-day mortality while three studies presented in-hospital mortality. In the meta-analysis using a random effects model (Figure 2), the permissive hypotension strategy demonstrated significant evidence of a survival benefit – a pooled odds ratio for mortality of 0.70 (95% CI 0.53 to 0.92). The I2 statistic was 0%, suggesting minimal statistical heterogeneity.

**Figure 2 – Forest Plot of Permissive Hypotension vs. Conventional Resuscitation**




### 2. *Health related quality of life :*

Tra le 5 revisioni sistematiche incluse, nessuna riporta l'outcome di interesse.

### 3. *Neurological outcome :*

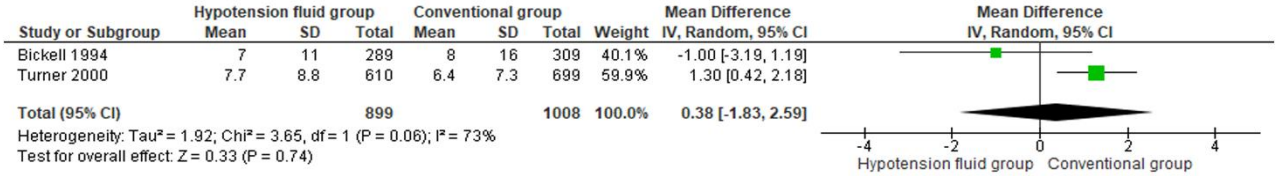
Tra le 5 revisioni sistematiche incluse, nessuna riporta l'outcome di interesse.

### *4. Length of intensive care stay*

Tra le 5 revisioni sistematiche incluse, Safiejko 2020 riporta l'outcome di interesse. Di seguito si riportano le analisi relative.

**Safiejko 2020**

The length of stay in the intensive care unit (ICU) was reported by two studies [16, 32]. The polled analysis did not show significant differences in the length of stay in ICU between the groups (MD = 0.38; 95% CI: –1.83–2.59; I2 = 73%; p = 0.74; Suppl. Fig. S3). Three studies indicated length of stay in hospital [16, 29, 32]. The difference between therapeutic groups was not statistically significant (MD = –0.82; 95% CI: –2.43–0.78; I2 = 0%; p = 0.32; Suppl. Fig. S4).




**Suppl. Fig. S3. Length of stay in ICU.**

### *5. Blood product use*

Tra le 5 revisioni sistematiche incluse, 4 riportano i dati di interesse (Duan 2015, Owattanapanich 2018, Safiejko 2020, Tran 2018). Tutte riportano metanalisi tranne Tran 2018 che identifica gli outcome *Globuli rossi concentrati* e *Cristalloidi* come secondari in una tabella descrittiva.

- Piastrine (Duan 2015 e in Safiejko 2020)
- Globuli rossi concentrati (Owattanapanich 2018, Safiejko 2020, Tran 2018)
- Plasma fresco (Safiejko 2020)
- Cristalloidi (Tran 2018)

## 5.1 Piastrine (Duan 2015 e in Safiejko 2020)

Le RS non includono gli stessi studi e risultano in effetti diversi.

### Duan 2015

The overall effect suggested that PLT value in LFR group was higher than that in RFR group (MD = 23.16; 95% CI = 6.41-39.91; P = 0.007)

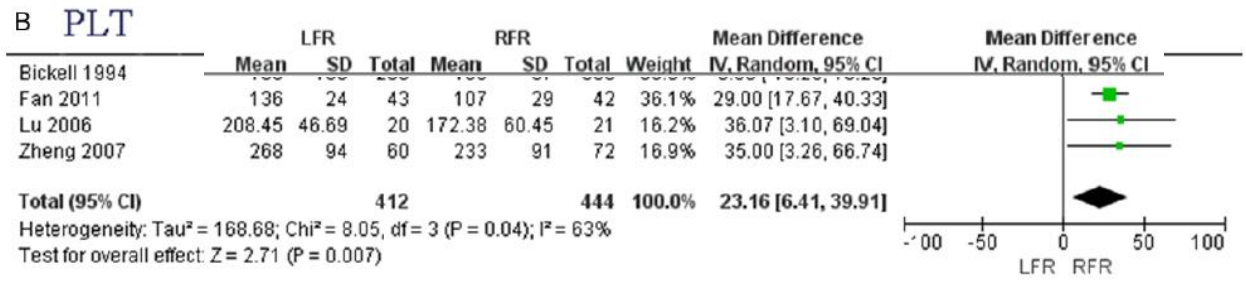
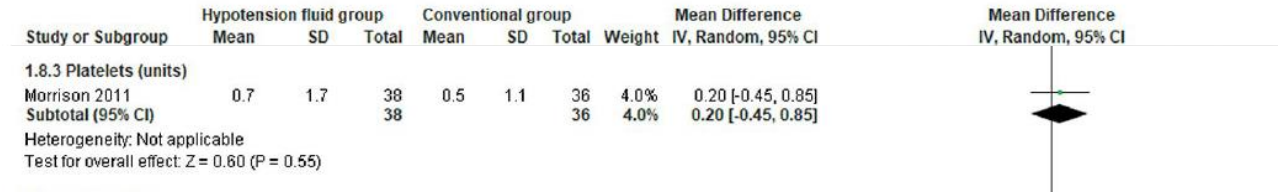



Figure 3. Forest plot illustrating the platelets blood index between LFR and RFR in hemorrhagic shock.
Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; MD, Mean difference; PLT, Platelets

### Safiejko 2020




## 5.2 Globuli rossi concentrati (PRBCs) (Owattanapanich 2018, Safiejko 2020, Tran 2018)

Le RS non includono gli stessi studi e risultano in effetti diversi.

### Owattanapanich 2018

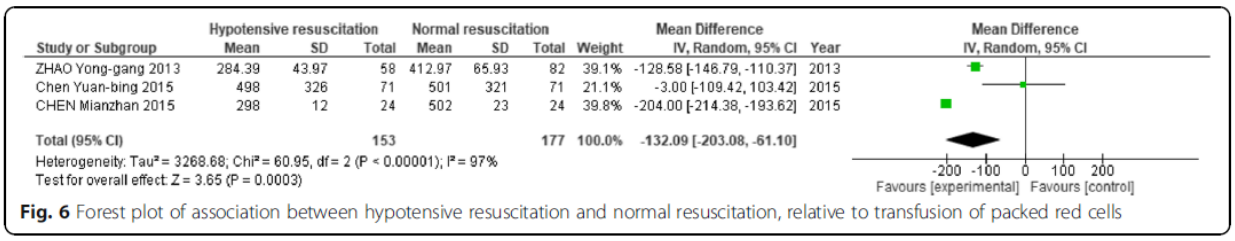
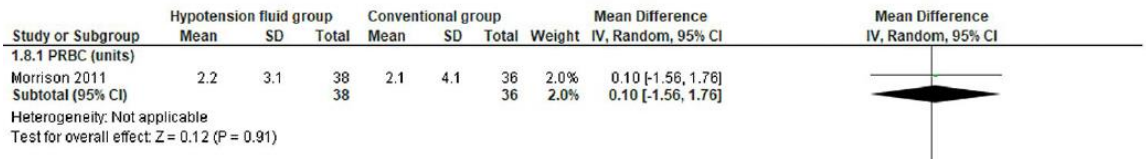



**Fig. 6** Forest plot of association between hypotensive resuscitation and normal resuscitation, relative to transfusion of packed red cells

### Safiejko 2020



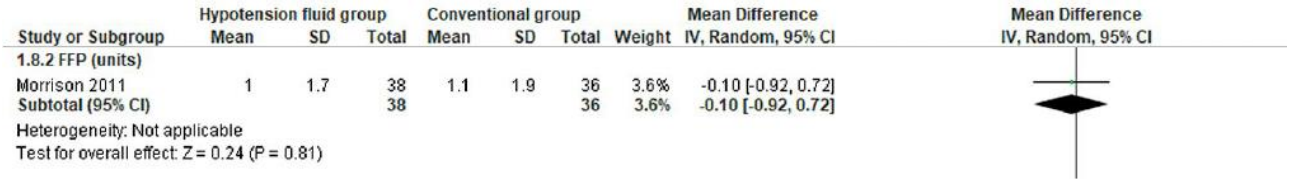
## Tran 2018

**Table 3 – Secondary Outcome Data**

| Study | Study Arm | PRBC Volume | Prehospital Crystalloid | ED Crystalloid Volume | Intraoperative Crystalloid | Estimated Blood Loss | Complications |
|---|---|---|---|---|---|---|---|
| Bickell (1994) | Control | 133 +/- 393 mL | 870 +/- 667 mL | 1608 +/- 1201 mL | 6772 +/- 4688 mL | 3127 +/- 4937 mL | Sepsis – 5.0%<br>Coagulopathy – 8.0%<br>Renal Failure – 4.0%<br>ARDS – 4.0% |
| | PH | 11 +/- 88 mL | 92 +/- 309 mL | 283 +/- 722mL | 6529 +/- 4863 mL | 2555 +/- 3546 mL | Sepsis – 5.0%<br>Coagulopathy – 7.0%<br>Renal Failure – 1.0%<br>ARDS – 1.0% |
| Carrick (2016) | Control | 1500 mL | NR | NR | 2000 mL | NR | Coagulopathy – 28.8%<br>Renal Failure – 12.1% |
| | PH | 1125 mL | | | 2200 mL | | Coagulopathy – 28.0%<br>Renal Failure – 14.7% |
| Dutton (2002) | Control | NR | NR | NR | NR | NR | NR |
| | PH | | | | | | |
| Morrison (2011) | Control | 2244 +/- 2466 mL | NR | NR | 3282 +/- 2010 mL | 3008 +/- 2948 mL | Coagulopathy – 61.1% |
| | PH | 1335 +/- 1812 mL | | | 2883 +/- 921 mL | 1964 +/- 2215 mL | Coagulopathy – 60.5% |
| Schreiber (2015) | Control | 270 +/- 620 mL | 500 +/- 350 mL | 1750 +/- 1570 mL | NR | NR | Renal Failure – 1% |
| | PH | 730 +/- 1730 mL | 230 +/- 190 mL | 990 +/- 1460 mL | | | Renal Failure – 3% |



## 5.3 Plasma fresco (Safiejko 2020)



## 5.4 Cristalloidi (Tran 2018)

**Table 3 – Secondary Outcome Data**

| Study | Study Arm | PRBC Volume | Prehospital Crystalloid | ED Crystalloid Volume | Intraoperative Crystalloid | Estimated Blood Loss | Complications |
|---|---|---|---|---|---|---|---|
| Bickell (1994) | Control | 133 +/- 393 mL | 870 +/- 667 mL | 1608 +/- 1201 mL | 6772 +/- 4688 mL | 3127 +/- 4937 mL | Sepsis – 5.0%<br>Coagulopathy – 8.0%<br>Renal Failure – 4.0%<br>ARDS – 4.0% |
| | PH | 11 +/- 88 mL | 92 +/- 309 mL | 283 +/- 722mL | 6529 +/- 4863 mL | 2555 +/- 3546 mL | Sepsis – 5.0%<br>Coagulopathy – 7.0%<br>Renal Failure – 1.0%<br>ARDS – 1.0% |
| Carrick (2016) | Control | 1500 mL | NR | NR | 2000 mL | NR | Coagulopathy – 28.8%<br>Renal Failure – 12.1% |
| | PH | 1125 mL | | | 2200 mL | | Coagulopathy – 28.0%<br>Renal Failure – 14.7% |
| Dutton (2002) | Control | NR | NR | NR | NR | NR | NR |
| | PH | | | | | | |
| Morrison (2011) | Control | 2244 +/- 2466 mL | NR | NR | 3282 +/- 2010 mL | 3008 +/- 2948 mL | Coagulopathy – 61.1% |
| | PH | 1335 +/- 1812 mL | | | 2883 +/- 921 mL | 1964 +/- 2215 mL | Coagulopathy – 60.5% |
| Schreiber (2015) | Control | 270 +/- 620 mL | 500 +/- 350 mL | 1750 +/- 1570 mL | NR | NR | Renal Failure – 1% |
| | PH | 730 +/- 1730 mL | 230 +/- 190 mL | 990 +/- 1460 mL | | | Renal Failure – 3% |

***IMPORTANT OUTCOMES***

### *1. Multi organ failure*

Tra le 5 revisioni sistematiche incluse, tre riportano l'outcome di interesse (Duan 2015, Owattanapanich 2018 e Safiejko 2020). Di seguito si riportano i dati relativi per ciascuna revisione sistematica.

**Duan 2015**

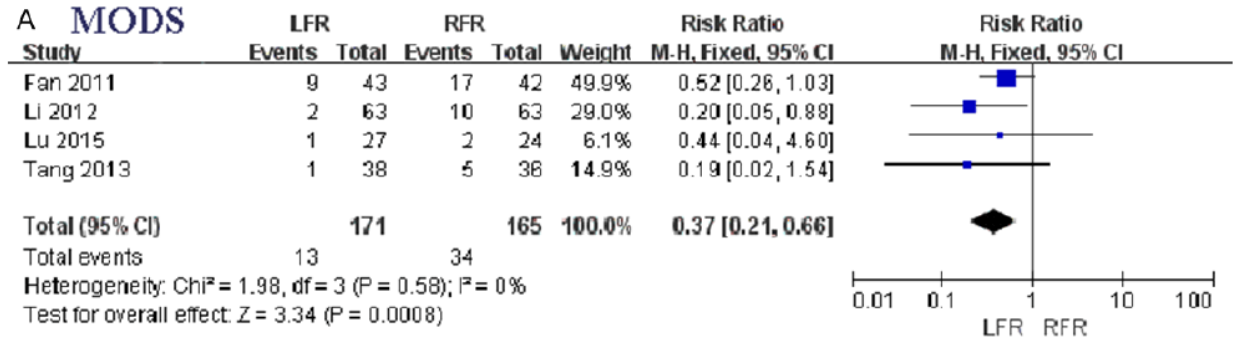



Figure 6. Forest plot illustrating main postoperative complications between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; M-H, Mantel-Haenszel; A. MODS, multiple organ dysfunction syndrome; B. ARDS, Acute Respiratory Distress Syndrome

**Owattanapanich 2018**

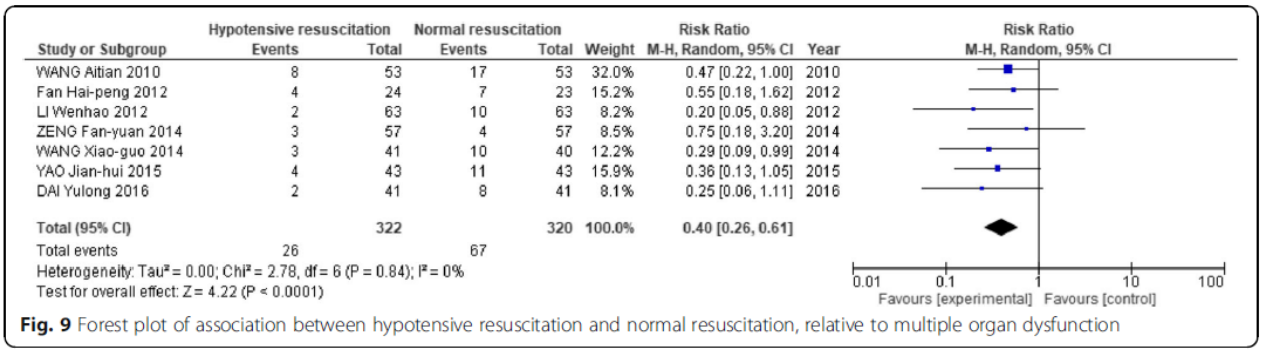



**Fig. 9** Forest plot of association between hypotensive resuscitation and normal resuscitation, relative to multiple organ dysfunction

**Safiejko 2020**

The pooled analysis showed that hypotension fluid resuscitation compared to conventional fluid resuscitation was associated with a lower risk of adverse events (10.8% vs. 13.4%, respectively; RR = 0.70; 95% CI: 0.59–0.83; I2 = 52%; p < 0.001). The use of hypotension versus conventional fluid resuscitation showed a higher incidence of anemia (74.3% vs. 68.6%), thrombocytopenia (33.6% vs. 29.4%) and acute renal failure (8.8% vs. 8.1%). In other types of adverse events the relationship was reversed, and the use of hypotension fluid resuscitation was associated with a lower risk of complications (Table 1).

**Table 1.** Comparison of hypotension and conventional fluid resuscitation relative to adverse events.

| | Number of trials | Hypotension fluid resuscitation | Conventional fluid resuscitation | RR or MD (95% CI) | P value | $I^2$ statistic, % |
|---|---|---|---|---|---|---|
| ARDS | 13 | 7.8% | 16.8% | 0.44 [0.34–0.58] | < 0.001 | 0% |
| Acute myocardial infarction | 1 | 1.3% | 1.5% | 0.88 [0.06–13.79] | 0.93 | – |
| Stroke | 1 | 0% | 3.0% | 0.18 [0.01–3.61] | 0.26 | – |
| Sepsis syndrome | 2 | 3.5% | 3.9% | 0.91 [0.42–1.98] | 0.82 | 0% |
| MODS | 10 | 8.6% | 21.6% | 0.42 [0.30–0.60] | < 0.001 | 0% |
| Any renal failure | 1 | 14.7% | 12.1% | 1.21 [0.52–2.83] | 0.66 | – |
| Acute renal failure | 8 | 8.8% | 8.1% | 0.99 [0.53–1.86] | 0.98 | 61% |
| Anemia | 2 | 74.3% | 68.6% | 1.11 [0.96–1.28] | 0.16 | 2% |
| Hypotension | 1 | 13.3% | 16.7% | 0.80 [0.36–1.76] | 0.58 | – |
| Coagulopathy | 3 | 15.7% | 15.8% | 0.95 [0.73–1.24] | 0.73 | 0% |
| Thrombocytopenia | 2 | 33.6% | 29.4% | 1.21 [0.64–2.28] | 0.56 | 54% |
| Pneumonia | 1 | 7.6% | 9.1% | 0.84 [0.49–1.43] | 0.52 | – |
| Deterioration in T-RTS | 1 | 7.4% | 7.9% | 0.93 [0.50–1.71] | 0.81 | – |
| Complications not specified | 1 | 7.5% | 8.6% | 0.88 [0.61–1.27] | 0.49 | – |

ARDS — acute respiratory distress syndrome; MORS — multiple organ dysfunction syndrome; MD — mean difference; RR — risk ratio

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

Tra le 5 revisioni sistematiche incluse, una revisione sistematica riporta propriamente l'outcome di interesse: Tran 2018. Mentre come outcome surrogato Duan 2015 riporta dati inerenti tempo di Prothrombin (PT) e tempo activated partial thromboplastin (APTT), quali parametri indicativi di coagulopatia e quindi difficolta' all'emostasi definitiva. Di seguito si riportano le analisi relative.

**Tran 2018**

La revisione di Tran 2018, identifica l'outcome di interesse in un solo RCT, Dutton 2002. Di segutio i dati relativi.

| Study | Country of Origin | Population | Trauma Centre Level | n | Mechanism | Time Period | Time to Hemostasis (Hours) * | Additional Study Eligibility Criteria | Intervention | Control |
|---|---|---|---|---|---|---|---|---|---|---|
| Dutton (2002) | USA | Civilian | Level 1 | 110 | Blunt and penetrating | Preoperative + ntraoperative | **2.57 +/- 1.46** |  Presenting directly from scene of injury  Excluded central nervous system injury impairing level of consciousness or motor function | 200 – 500 mL bolus for SBP <70 mmHg and maintain SBP >70mmHg | 200 – 500 mL bolus for SBP <100 mmHg SBP >100mmH |

*see table 1 of RCT Dutton 2002:

Table 1 of RCT Dutton 2002

**Table 1** Outcomes of Patients Enrolled in the Fluid Resuscitation in Trauma Study, by Target Blood Pressure Group (Means ± SD)

| | SBP > 100 mm Hg | SBP = 70 mm Hg | *p* Value |
|---|---|---|---|
| Patients enrolled | 55 | 55 | |
| Average SBP during bleeding (mm Hg) | 114 ± 12 | 100 ± 17 | <0.001 |
| Length of active hemorrhage (h) | 2.97 ± 1.75 | 2.57 ± 1.46 | 0.20 |
| Died | 4 | 4 | |
| Average ISS | 19.55 ± 11.6 | 23.91 ± 13.8 | 0.08 |
| Predicted survival rate (TRISS) | 94.0 ± 12% | 90.2 ± 17% | 0.18 |
| Actual survival rate (%) | 92.7 | 92.7 | |

**Duan 2015** - tempo di Prothrombin (PT) e tempo activated partial thromboplastin (APTT)

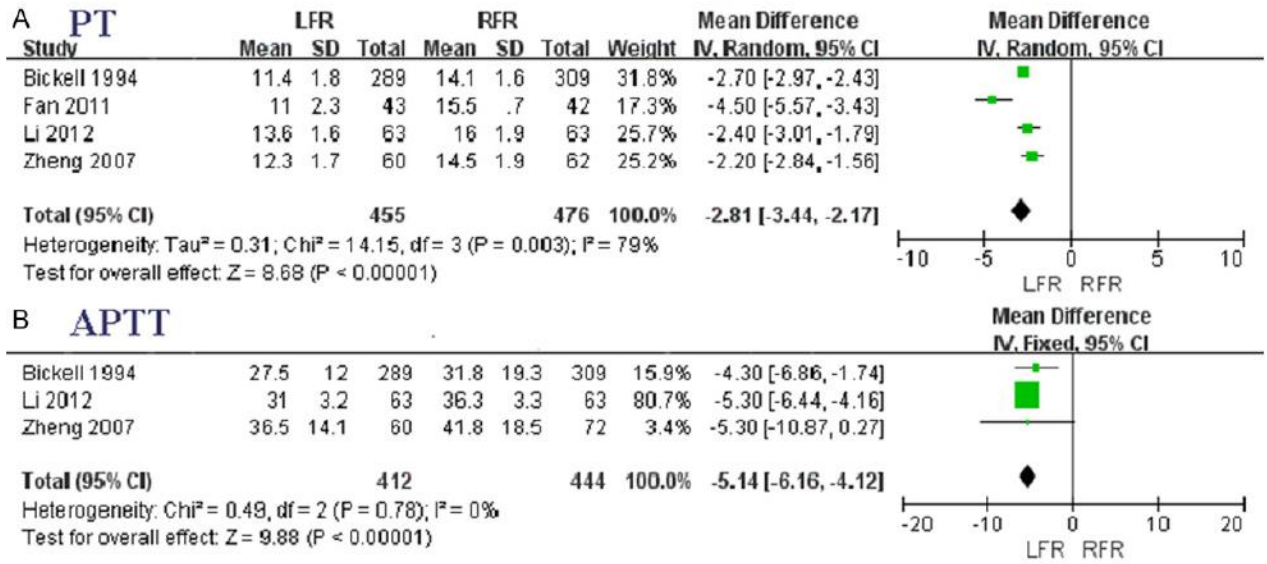



Figure 4. Forest plot illustrating the blood coagulation function between LFR and RFR in hemorrhagic shock. Abbreviation: LFR, limited fluid resuscitation; RFR, regular fluid resuscitation; CI, confidence interval; MD, Mean difference; A. PT, Prothrombin Time; B. APTT, activated partial thromboplastin time.

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

Tra le 5 revisioni sistematiche incluse, nessuna riporta l'outcome di interesse.

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## Appendice D. Valutazione della qualità metodologica degli studi inclusi

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero.*

**Systematic reviews:** based on the pre-defined criteria (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 studied for inclusion), we reported the overalapping of retrieved SRs and the quality judgement using the AMSTAR II .

Overall all SRs ranged from critically low to moderate quality.

**Tabella 1**. Overlapping fra le SRs incluse per PICO questions and included studies

| | SR | Albreiki 2017, Eur J Trauma Emerg Surg | Duan 2015, Int J Clin Exp Med | Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine | Safiejko 2020,Cardiology Journal | Tran 2018,Journal of Trauma and Acute Care Surgery |
|---|---|---|---|---|---|---|
| Number of studies and update searches | | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015 | 20 trials, 4 observational studies up to january 2018 | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| Pico questions and characteristics | **Population** | adult patients (aged ≥ 15 years) of blunt or penetrating trauma, with one or more documented episode of hypotension (systolic blood pressure ≤ 90 mmHg); | The trauma patients in the study presented with a common clinical syndrome - hemorrhagic shock | adult patients aged older than 18 years who had traumatic hemorrhagic shock and a systolic blood pressure below 90mmHg. | traumatic hemorrhagic shock patients | adult patients with penetrating or blunt traumatic injury and suspicion of hemorrhage. Civilian or military patient populations were both eligible. |
| | **Intervention and comparison** | normotensive and hypotensive trauma | fluid resuscitation | conventional fluid resuscitation with normotension (liberal fluid resuscitation) versus hypotensive resuscitation (limited fluid resuscitation). | hypotension versus conventional fluid resuscitation | permissive hypotension vs. conventional resuscitation |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **Outcomes** | the survival rate between participants resuscitated with either low or large fluid administration, or that measure the number of deaths in patients managed with fluid resuscitation | mortality, the blood routine index (hemoglobin, Hb; Platelets, PLT; Hematocrit, Hct), blood coagulation function (Prothrombin Time, PT; activated partial thromboplastin time, APTT), blood gas analysis (base excess, BE; blood lactic acid, BLA) and the main postoperative complications, such as MODS (multiple organ dysfunction syndrome) and ARDS (Acute Respiratory Distress Syndrome). | The primary outcome was all-cause mortality, as reported by the authors of the included studies. The secondary outcomes included the rates of the following morbidities: acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and multiple organ dysfunction (MODS). Other secondary outcomes included the fluid resuscitation volume and the transfusion of packed red cells. | Mortality, adverse events,Fluid balance and transfusion requirements, lenght of stay | The primary outcome was 30-day or in-hospital mortality. Secondary outcomes included blood product utilization, estimated blood loss and in-hospital complications. |
| | **language** | english | no language restriction | no language restriction | english | no language or date restrictions |
| | **setting** | studies conducted on humans and in clinical settings, either in pre-hospital or in-hospital critical care | | | | pre-operative and intraoperative resuscitation strategies |
| | **study design** | randomized and retrospective studies | randomized or quasi-randomized | randomized controlled trials (RCTs) and cohort studies | randomized controlled trials (RCTs) and quasi-randomized trials. | randomized controlled trials and quasi-randomized trials |
| | **EXCLUSION criteria** | studies on hypotensive resuscitation in patients with traumatic brain injury (TBI), which might affect the identification of the real cause of death among participants | The study in which patients were threatened by traumatic brain injury (TBI) | Excluded were studies of patients who were pregnant or had traumatic brain injuries, | | suspected traumatic brain injury |
| | | 5 | 11 | 20 | 28 | 5 |

**Tabella 2**. AMSTAR 2 – Methodological quality across systematic reviews

| | **Albreiki 2017** | **Duan 2015** | **Owattanapanich 2018** | **Safiejko 2020** | **Tran 2018** |
|---|---|---|---|---|---|
| **OVERALL QUALITY** | 5 trials and 5 retrospective studies, up to may 2016 Critically low | 11 trials, up to january 2015 Critically low | 20 trials, 4 observational studies up to january 2018 Critically low | 28 trials, up to june 2020 Critically low | 5 trials, up to may 2017 Critically low |
| 1-Question and inclusion | yes | yes | yes | yes | yes |
| 2-Protocol | no | no | no | no | yes |
| 3-Study design | no | no | no | no | yes |
| 4-Comprehensive search | yes | yes | yes | yes | yes |
| 5-Study selection | yes | yes | yes | yes | yes |
| 6-Data extraction | yes | yes | yes | yes | yes |
| 7-Excluded studied justification | no | no | partially yes | no | partially yes |
| 8-Included studied details | partially yes | partially yes | yes | no | 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 | NA | yes | no | yes | yes |
| 12-Rob on meta-analyses | NA | no | no | no | no |
| 13-Rob on individual studies | no | no | no | no | no |
| 14-Explanation for heterogeneity | no | no | yes | no | yes |
| 15-Publication bias | NA | yes | yes | no | no |
| 16-Conflict of interest | yes | yes | yes | yes | yes |
| tot yes | 6 | 8 | 9 | 7 | 11 |
| **no critical flaws** | **2 out of 6** | **3 out of 6** | **3 out of 6** | **2 out of 6** | **3 out of 6** |

* Judgements:
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.

## Appendice E. Tabelle delle evidenze

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero.*

**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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SR identification | | SR | **Albreiki 2017, Eur J Trauma Emerg Surg** | **Duan 2015, Int J Clin Exp Med** | **Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine** | **Safiejko 2020,Cardiology Journal** | **Tran 2018,Journal of Trauma and Acute Care Surgery** |
| | | characteristics | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015; publication bias assessed (low risk) | 20 trials, 4 observational studies up to january 2018; publication bias assessed (high risk) | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| **critical** | 1 | **Mortality**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency<br>publication bias | no metanalysis<br>5 RCTs, n=1157;<br>21.57% (hypotensive) versus 28.6% (aggressive) | 9 RCTs, n=754;<br>RR = 0.67; 95% CI = 0.56,0.81, I2=90.9<br>->subgroup analysis countries<br>$I^2$=0: America RR= 0.81; 95% CI = 0.66,1.0, China RR=0.35; 95% CI = 0.22,0.55<br>serious<br>serious<br>serious<br>not serious<br>none | 24 RCTs+observational studies, n = 1473;<br>RR: 0.50; 95% CI= 0.40,0.61, $I^2$=27%<br>serious<br>not serious<br>serious<br>serious<br>very serious | 28 RCTs, n= 4503;<br>RR = 0.58; 95% CI= 0.51,0.66; $I^2$ = 37%;<br>serious<br>not serious<br>very serious<br>not serious<br>serious | 5 RCTs, n=1152 ;<br>RR = 0.70; 95% CI= 0.53,0.92; $I^2$= 0%;<br>serious<br>serious<br>serious<br>not serious<br>none |
| | | **QUALITY of EVIDENCE** | ONLY DESCRIPTIVE | VERY LOW | VERY LOW | VERY LOW | VERY LOW |
| | 2 | **Health related-quality of life**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency<br>publication bias<br>**QUALITY of EVIDENCE** | not assessed | not assessed | not assessed | not assessed | not assessed |

| SR identification | | SR | Albreiki 2017, Eur J Trauma Emerg Surg | Duan 2015, Int J Clin Exp Med | Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine | Safiejko 2020,Cardiology Journal | Tran 2018,Journal of Trauma and Acute Care Surgery |
|---|---|---|---|---|---|---|---|
| | | characteristics | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015; publication bias assessed (low risk) | 20 trials, 4 observational studies up to january 2018; publication bias assessed (high risk) | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| | 3 | **Neurological outcome**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency<br>publication bias<br><br>**QUALITY of EVIDENCE** | not assessed | not assessed | not assessed | not assessed | not assessed |
| | 4 | **Length of ICU stay**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency<br>publication bias<br>**QUALITY of EVIDENCE** | not assessed | not assessed | not assessed | 2 RCTs, n=1907; MD = 0.38; 95% CI: –1.83,2.59; $I^2$ = 73%; p =0.74;<br>serious<br>very serious<br>very serious<br>not serious<br>serious<br>VERY LOW | not assessed |
| | 5 | **Blood produce use**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency | | | | | |

| SR identification | | SR | Albreiki 2017, Eur J Trauma Emerg Surg | Duan 2015, Int J Clin Exp Med | Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine | Safiejko 2020,Cardiology Journal | Tran 2018,Journal of Trauma and Acute Care Surgery |
|---|---|---|---|---|---|---|---|
| | | characteristics | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015; publication bias assessed (low risk) | 20 trials, 4 observational studies up to january 2018; publication bias assessed (high risk) | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| | | publication bias | | | | | |
| | | **QUALITY of EVIDENCE** | | | | | |
| | 5.1 | **platatelets** | not assessed | 4 RCTs, n=856; MD =23.16; 95% CI = 6.41,39.91,$I^2$=63% | not assessed | 1 RCT, n=774 MD=0.20; CI 95% CI=-0.45, 0.65 | not assessed |
| | | risk of bias | | serious | | serious | |
| | | imprecision | | serious | | not serious* | |
| | | indirectness | | serious | | very serious | |
| | | inconsistency | | not serious | | not serious* | |
| | | publication bias | | none | | serious | |
| | | **QUALITY of EVIDENCE** | | VERY LOW | | VERY LOW | |
| | 5.2 | **transfusion of packed red cells (PRBCs)** | not assessed | not assessed | 3 RCT+observational studies, n=330 MD: -132.09; 95% CI= -203.08,-61.10, $I^2$=97% | 1 RCT, n=74 MD=0.10; 95% CI = -1.56,1.76 | descriptive table (4 RCTs) |
| | | risk of bias | | | serious | serious | |
| | | imprecision | | | not serious | serious* | |
| | | indirectness | | | serious | very serious | |
| | | inconsistency | | | very serious | not serious * | |
| | | publication bias | | | very serious | serious | |
| | | **QUALITY of EVIDENCE** | | | VERY LOW | VERY LOW | ONLY DESCRIPTIVE |
| | 5.3 | **frozen fresh plasma (FFP)** | | | | 1 RCT, n=74 MD=-0.10; 95% CI = -0.92,0.72 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SR identification | | SR | **Albreiki 2017, Eur J Trauma Emerg Surg** | **Duan 2015, Int J Clin Exp Med** | **Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine** | **Safiejko 2020,Cardiology Journal** | **Tran 2018,Journal of Trauma and Acute Care Surgery** |
| | | characteristics | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015; publication bias assessed (low risk) | 20 trials, 4 observational studies up to january 2018; publication bias assessed (high risk) | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| | | risk of bias | | | | serious | |
| | | imprecision | | | | serious* | |
| | | indirectness | | | | very serious | |
| | | inconsistency | | | | not serious* | |
| | | publication bias | | | | serious | |
| | | **QUALITY of EVIDENCE** | | | | VERY LOW | |
| | 5.3 | **Cristalloids** | not assessed | not assessed | not assessed | not assessed | descriptive table (2 RCTs) |
| | | risk of bias | | | | | |
| | | imprecision | | | | | |
| | | indirectness | | | | | |
| | | inconsistency | | | | | |
| | | publication bias | | | | | |
| | | **QUALITY of EVIDENCE** | | | | | ONLY DESCRIPTIVE |
| important | 1 | **multiple organ dysfunction syndrome** | not assessed | 4 RCTs, n=342; RR =0.37; 95% CI = 0.21,0.66, $I^2$=0% | 7 RCTs+observ, n=642; RR =0.40; 95% CI = 0.26,0.61, $I^2$=0% | 10 RCTs RR=0.42 95%; CI = 0.30,0.60, $I^2$=0 | not assessed |
| | | risk of bias | | serious | serious | serious | |
| | | imprecision | | serious | serious | serious | |
| | | indirectness | | serious | serious | very serious | |
| | | inconsistency | | not serious | serious | not serious | |
| | | publication bias | | none | very serious | serious | |
| | | **QUALITY of EVIDENCE** | | VERY LOW | VERY LOW | VERY LOW | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SR identification | | SR | **Albreiki 2017, Eur J Trauma Emerg Surg** | **Duan 2015, Int J Clin Exp Med** | **Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine** | **Safiejko 2020,Cardiology Journal** | **Tran 2018,Journal of Trauma and Acute Care Surgery** |
| | | characteristics | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015; publication bias assessed (low risk) | 20 trials, 4 observational studies up to january 2018; publication bias assessed (high risk) | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| | 2 | **Time to definitive control of haemorrhage**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency<br>publication bias | not assessed | not assessed | not assessed | not assessed | Defined as Time to Hemostasis (Hours): 1 RCT, 2.57 +/- 1.46 (intervention and control group) |
| | | **QUALITY of EVIDENCE** | | | | | ONLY DESCRIPTIVE |
| | 2.1 | **PT**<br>risk of bias<br>imprecision<br>indirectness<br>inconsistency<br>publication bias | not assessed | 4 studies, n=931;<br>MD=-2.81 95% CI =-3.44, -2.17, $I^2$=79%<br>serious<br>not serious<br>serious<br>serious<br>none | not assessed | not assessed | not assessed |
| | | **QUALITY of EVIDENCE** | | VERY LOW | | | |
| | 2.2 | **APTT**<br>risk of bias<br>imprecision | not assessed | 3 studies, n=856;<br>MD=-5.14 95% CI =-6.16, -4.12, $I^2$=0%<br>serious<br>not serious | not assessed | not assessed | not assessed |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SR identification | | SR | **Albreiki 2017, Eur J Trauma Emerg Surg** | **Duan 2015, Int J Clin Exp Med** | **Owattanapanich 2018,Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine** | **Safiejko 2020,Cardiology Journal** | **Tran 2018,Journal of Trauma and Acute Care Surgery** |
| | | characteristics | 5 trials and 5 retrospective studies, up to may 2016 | 11 trials, up to january 2015; publication bias assessed (low risk) | 20 trials, 4 observational studies up to january 2018; publication bias assessed (high risk) | 28 trials, up to june 2020 | 5 trials, up to may 2017 |
| | | indirectness | | serious | | | |
| | | inconsistency | | not seriuos | | | |
| | | publication bias | | none | | | |
| | | **QUALITY of EVIDENCE** | | 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. Bibliografia degli studi inclusi.

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero.*

**Systematic reviews:**


1. Albreiki, M., Voegeli, D., https://orcid.org, I.O., Albreiki, M. & https://orcid.org, I.O. Permissive hypotensive resuscitation in adult patients with traumatic haemorrhagic shock : a systematic review. European journal of trauma and emergency surgery : official publication of the European Trauma Society 44, 191-202.
2. Duan, C., Li, T. & Liu, L. Efficacy of limited fluid resuscitation in patients with hemorrhagic shock : a meta - analysis. International journal of clinical and experimental medicine 8, 11645-11656 (2015).
3. Owattanapanich, N., Sirikun, J., Chittawatanarat, K. & Benyakorn, T. Risks and benefits of hypotensive resuscitation in patients with traumatic hemorrhagic shock : a meta - analysis. Scandinavian journal of trauma, resuscitation and emergency medicine 26, 107.
4. Safiejko, K., https://orcid.org, I.O., Smereka, J., et al. Effectiveness and safety of hypotension fluid resuscitation in traumatic hemorrhagic shock : a systematic review and meta - analysis of randomized controlled trials. Cardiology journal 10, 1897-5593 (2020).
5. Tran, A., re, Yates, J., Lau, A., Lampron, J. & Matar, M. Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock : A systematic review and meta - analysis of randomized controlled trials. The journal of trauma and acute care surgery 84, 802-808.


**Randomized Controlled Trials:**


1. Carrick Matthew, M., Morrison Catherine, A., Tapia Nicole, M., et al. Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma : Early termination of a randomized prospective clinical trial. The journal of trauma and acute care surgery 80, 886-896.
2. Schreiber, M.A., Meier, E.N., Tisherman, S.A., et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. The journal of trauma and acute care surgery 78, 687-695; discussion 695-687 (2015).

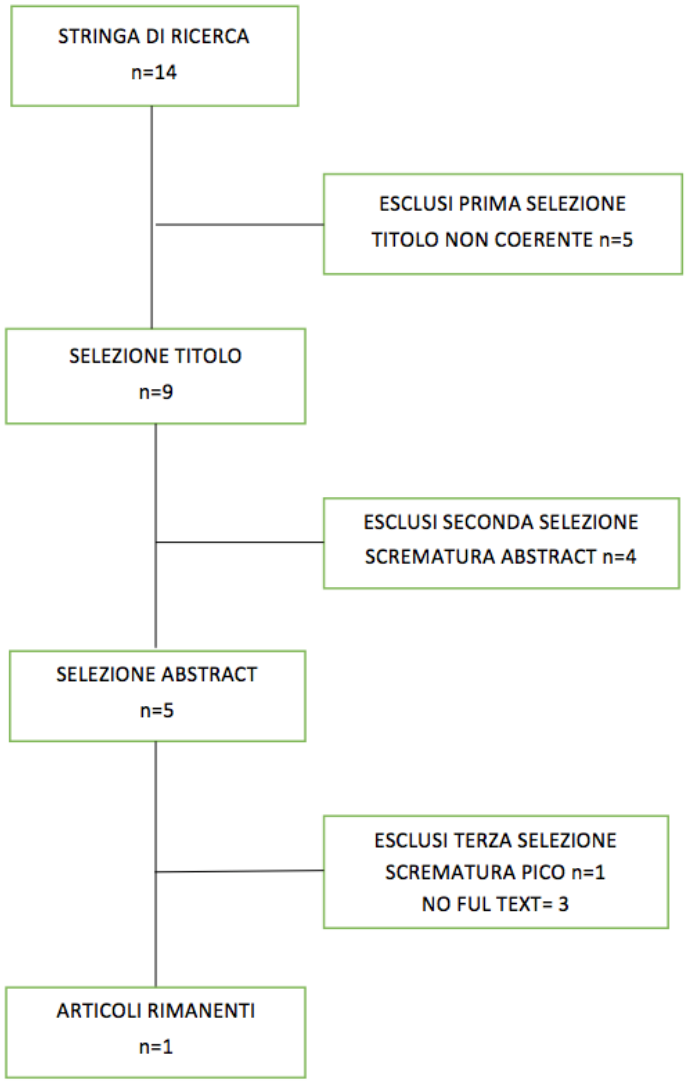
## Appendice G. Costi e valutazioni economiche.

*CQ11. Gestione dell'emorragia. Fluid resuscitation in setting pre-ospedaliero..*

**COSTI**

E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati individuati 14 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; (3) di cui non fosse disponibile il full text; (4) che fossero solamente presentazioni di abstract a conferenze. Che presenta una revisione delle evidenze di efficacia e di costo efficaciatrauma in un setting di pre ospedalizzazione. (Dretzke et al.2004).
In questo lavoro sono riportati costi dei fluidi e dei materiali di consumo secondo la prospettiva del National Health Service britannico.

**Figura 1**. Flow chart revisione della letteratura analisi dei costi



***Contesto internazionale***

Le tabelle seguenti mostrano il costo dei fluidi e dei kit endovena, così come risulta dalla revisione di Dretzke (2004). È da notare che tali dati si riferiscono al 2004, e quindi sono da reputarsi obsoleti.

| *Costi dei fluidi* | | |
|---|---|---|
| Salina 0.9% (500ml) | £0.38 | NHS Blood and Transplant Price List 2012 to 2013 |
| Salina 0.9% (1l) | £0.65 | NHS Blood and Transplant Price List 2012 to 2013 |
| Hartman (500ml) | £0.51 | NHS Blood and Transplant Price List 2012 to 2013 |
| Haemaccel (500ml) | £3.71 | NHS Blood and Transplant Price List 2012 to 2013 |
| Gelofusine (1l) | £9.45 | Details available from the authors upon request |
| Dextran 70 (500ml) | £4.78 | Finance Department, TARN participating hospital |
| Dextran 40 (500ml) | £4.56 | Finance Department, TARN participating hospital |
| Hetastarch | £15.57 | Finance Department, TARN participating hospital |

| *Costi del kit IV* | | |
|---|---|---|
| IV set (cannula…) | £1.23 | NHS Blood and Transplant Price List 2012 to 2013 |
| | £1.31 | NHS Blood and Transplant Price List 2012 to 2013 |
| | £1.32 | NHS Blood and Transplant Price List 2012 to 2013 |
| Cannula +saline flush | £1.11 | NHS Blood and Transplant Price List 2012 to 2013 |
| Cannula (Sharp save) | £2.36 | Details available from the authors upon request |

È possibile notare come i costi mostrati nella tabella precedente siano relativi al 2004 e quindi di molto difficile applicazione rispetto al contesto attuale.

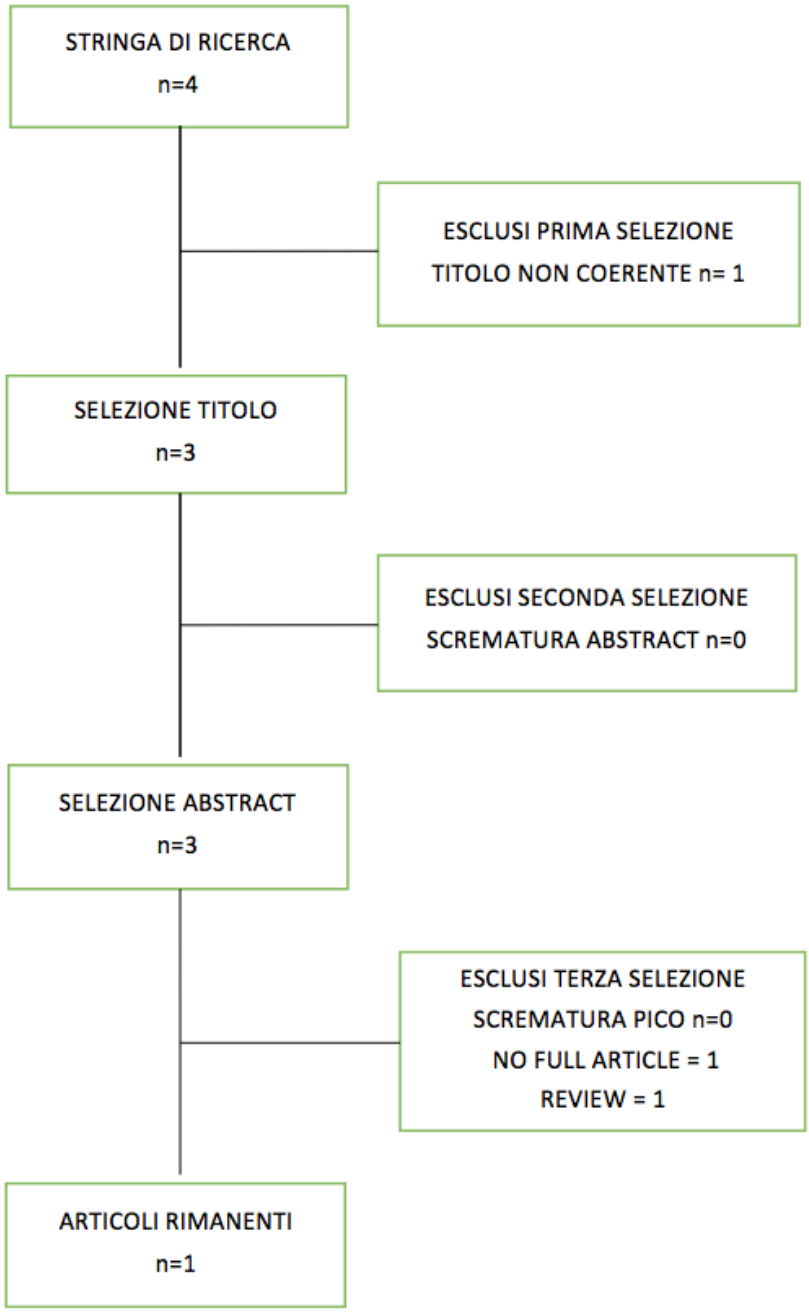
***Contesto nazionale***

E'stata effettuata una ricerca su database e documentazione riportante capitolati di gara inerenti aziende ospedaliere ed aziende sanitarie locali per reperire i prezzi dei fluidi e dei materiali di consumo necessari alla loro somministrazione. Sono stati reperiti alcuni dati che dimostrano come in molti casi non sia possibile reperire dati coerenti con quelli mostrati dalla evidenza di letteratura poiché molte marche in Italia non sono in commercio. Inoltre i nomi commerciali delle soluzioni disponibili nel nostro Paese, sono diversi.
In generale i prezzi delle soluzioni saline reperite variano dai € 0,20 ai € 0,70, mentre la media dei prezzi in gara dei fluidi si attesta a 5,5 ogni 500 millilitri.
Anche per quanto riguarda i prezzi delle cannule è stata effettuata una ricerca nella documentazione relativa a i capitolati di gara delle aziende sanitarie e delle aziende ospedaliere italiane. Esistono molte tipologie di cannule ed il prezzo medio è risultato pari ad € 1,5 per ogni kit.

## COSTO EFFICACIA

E'stata effettuata una revisione sistematica con una ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati individuati 4 records, da cui è stato incluso 1 solo studio (Turner et al., 2000).

**Figura 2.** Flow chart revisione della letteratura analisi costo-efficacia



Lo studio di Turner et al. (2000), ha condotto una valutazione di costo-beneficio basato su un RCT. La prospettiva considerata è quella della società. E' stato specificato un orizzonte temporale preciso ma il trial aveva una durata di 6 mesi. Lo studio confrontava due protocolli alternativi: il primo che prevedeva la somministrazione dei fluidi IV sulla scena del trauma e l'altro la somministrazione in ospedale. Sono state identificate, misurate e valorizzate le risorse differenziali fra i due protocolli, ma non sono presenti distinzioni fra tipologie di risorse, in quanto i costi sono riportati in forma aggregata. E'stata inoltre condotta una analisi di sensibilità deterministica ad una via considerando il doppio della deviazione standard osservata durante il trial. I risultati quantificavano i costi nel protocollo che prevedeva la somministrazione dei fluidi in un setting preospedaliero pari a 419, mentre i costi del protocollo che prevedeva la somministrazione dei fluidi in ospedalizzazione era pari a 416. In generale non si verificavano differenze statisticamente significative nei costi dei due protocolli. I dati di efficacia, aggiustati per diversi fattori prognostici (età, gravità e stato di coscienza del paziente sulla scena del trauma), non riportavano differenze statisticamente significative. Di conseguenza, gli autori concludevano che i protocolli fossero equivalenti.

## 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 della qualità metodologica 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*

Sebbene la qualità dello studio selezionato sia da considerarsi buona (75% di score riportato din base alla checklist CHEERS), mancano una serie di informazioni molto rilevanti: una proiezione dei risultati su una popolazione piu' ampia, una proiezione temporale aldilà dell'orizzonte temporale del trial, ed in generale un'analisi probabilistica multivariata. Inoltre, i dati di assorbimento delle risorse sono riportati solo in parte. Infine, lo studio no riporta dati inerenti la qualità della vita, anche se le differenze nei parametri di efficacia sono pressoché nulle, rendendo quindi qualsiasi ulteriore analisi superflua.

Anche se la valutazione della generalizzabilità delle evidenze riportate (Tabella 10.) restituisce come esito finale la specificità dei risultati relativamente al contesto di studio (britannico), le differenze nulle riguardo all'efficacia ed il basso costo dei fluidi, fanno propendere per una accettazione dei risultati come validi anche per il contesto italiano, di conseguenza, dal punto di vista delle evidenze di costo efficacia, si può asserire che non esiste differenza fra la somministrazione di fluidi in preospedalizzazione rispetto alla somministrazione in regime di ospedalizzazione.

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

| **Section/item** | **Turner et al. 2000** |
|---|---|
| ***Title and abstract*** | |
| Title | 1 |
| Abstract | 1 |
| ***Introduction*** | |
| Background and objectives | 1 |
| ***Methods*** | |
| Target population and groups | 1 |
| Setting and location | 1 |
| Study perspective | 1 |
| Comparators | 1 |
| Time horizon | 1 |
| Discount rates | 0 |
| Choice of health outcomes | 1 |
| Measurement of effectiveness | 1 |
| Measurement and evaluation of preference based outcomes | 0 |
| Estimating resources and cost | 1 |
| Currency and conversion | 1 |
| Choice of model | 0 |
| Assumptions | 0 |
| Analytic methods | 1 |
| ***Results*** | |
| Study parameters | 1 |
| Incremental costs and outcomes | 0 |
| Characterizing uncertainty | 1 |
| Characterizing heterogeneity | 1 |
| ***Discussion*** | |
| Study findings, limitations, generalizability, and current knowledge | 1 |
| ***Other*** | |
| Source of funding | 1 |
| Conflict of interest | 1 |
| **Total** | 75,00% |

**Tabella 10.** Valutazione della generalizzabilità delle evidenze economiche

| ITEMS FOR GENERALIZABILITY | Turner et al. 2000 |
|---|---|
| multicenter study (only for trial based) | 0 |
| context and description of the alternatives | 1 |
| complete reporting of the baseline characteristics of the study sample | 1 |
| adoption of a broad study perspective | 1 |
| clinical and cost data referring to the entire population | 1 |
| preference data relevant to the study populatiion | 0 |
| presence of quantitatiive/qualitative analyses perfored to evaluate the variability of results | 0 |
| clear justification of the model structure and parameters (only for models) | 0 |
| presence of a stochastic analysis to explore uncertainty (only for models) | 0 |
| reporting of epideiology (f relevant) | na |
| reported source of utility data | 0 |
| separate reporting of resources and unit costs | 0 |
| RESULT | context specific |

## References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