Raccomandazioni 12-13 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.

Novembre 2020

SOMMARIO

Lista delle raccomandazioni formulate

Quesito 7: Il posizionamento del REBOA (Resuscitative Endovascular Balloon Occlusion of the Aorta) è efficace dal punto di vista clinico e dei costi per il controllo temporaneo dell'emorragia grave nei pazienti con Trauma Maggiore?

Raccomandazione 12. Nel paziente con Trauma Maggiore e con ipotensione da shock emorragico non vi è indicazione all'utilizzo del REBOA se non nell'ambito di adeguati programmi di sperimentazione [raccomandazione forte, qualità delle prove molto bassa].

Raccomandazione 13. In pazienti in arresto/peri-arresto cardiocircolatorio da cause emorragiche, presumibilmente sottodiaframmatiche, è preferibile l'utilizzo del REBOA alla toracotomia resuscitativa come misura temporanea in attesa del controllo definitivo dell'emorragia [raccomandazione condizionata, qualità delle prove molto bassa].

Il panel di esperti ha formulato le due raccomandazioni 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 seguenti appendici:

- 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.

Nel corso del meeting del 9 settembre 2020 il panel, preso atto dei commenti degli stakeholder, ha ritenuto di dover modificare la raccomandazione n. 13. Il report della consultazione pubblica, **LGTM_Report consultazione stakeholders Raccomandazione 12 e 13_DEF**, è disponibile al seguente link:

https://www.iss.it/documents/20126/8404337/LGTM-consultazione-Racc12-13_report_def.pdf

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 seguente link:
https://www.iss.it/documents/20126/8404212/LGTM_Racc1_4_def

EtD Framework - Quesito clinico n. 7

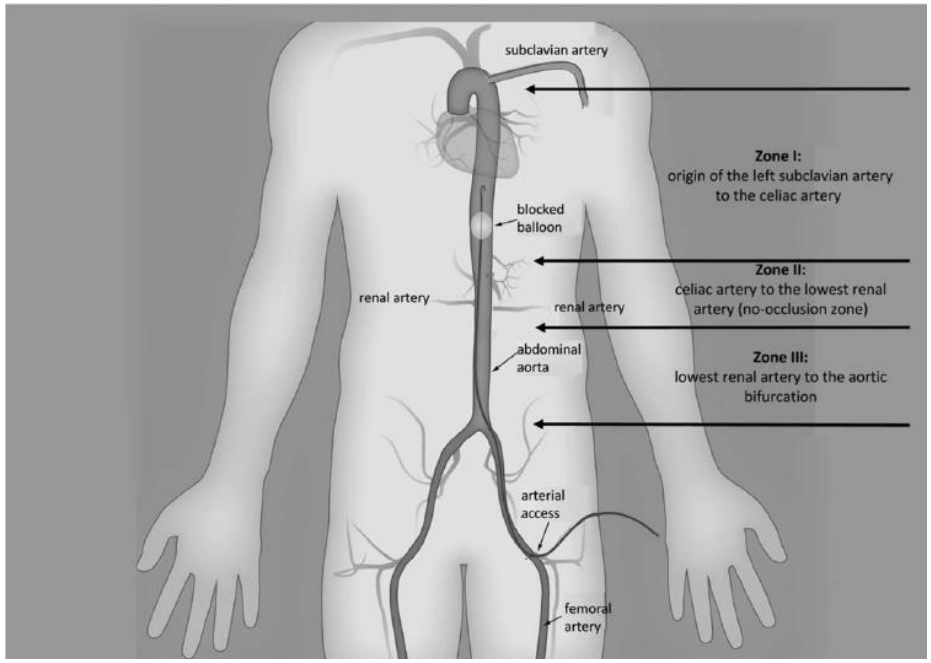
QUESITO 7. Il posizionamento del REBOA (Resuscitative Endovascular Balloon Occlusion of the Aorta) è efficace dal punto di vista clinico e dei costi per il controllo temporaneo dell'emorragia grave nei pazienti con Trauma Maggiore?	
	Bambini, giovani e adulti affetti da TRAUMA in fase di rianimazione preospedaliera, in pronto soccorso e in sala operatoria.
INTERVENTO:	REBOA – Resuscitative Endovascular Balloon Occlusion.
CONFRONTO:	Resuscitative Thoracotomy (toracotomia resuscitativa-RT)/ No REBOA.
ESITI PRINCIPALI:	**Critici** 1. Mortalità a 24 ore, 30 giorni/1 mese. 2. Volume degli emocomponenti. 3. Qualità della vita correlata alla salute. 4. Eventi avversi (ad es., amputazione). 5. Controllo dell'emorragia in emergenza. **Importanti** 1. Mortalità a 12 mesi. 2. Miglioramento dell'emodinamica (pressione sanguigna e frequenza cardiaca). 3. Fallimento della tecnica REBOA.
SETTING:	Ospedaliero e pre-ospedaliero (incluso il militare). Considerando la paucità degli studi in letteratura, si prendono in esame studi in Emergency Department e poi valutati per limitata generalizzabilità per la contestualizzazione nel pre-ospedaliero (indirecteness). Siccome le indicazioni per l'implementazione del REBOA dipendono dalle condizioni del paziente e dal setting, sono state indagate le seguenti comparazioni: REBOA vs Resuscitative Thoracotomy (RT); REBOA vs RT+REBOA; REBOA vs NO REBOA.
PROSPETTIVA:	Popolazione, SSN: • organizzazione ed erogazione dei servizi per la gestione dei pazienti con trauma; • rete regionale per il trauma; • personale sanitario dei servizi di emergenza territoriale.
CONFLITTI DI INTERESSE	La policy ISS relativa alla dichiarazione e gestione del conflitto di interessi è stata applicata e non è stato identificato nessun interesse rilevante o potenzialmente rilevante. Tutti i membri del panel presenti alla riunione hanno votato, determinando la direzione e la forza della raccomandazione.

VALUTAZIONE

Problema

Il problema è una priorità?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ○ Probabilmente si ○ Si ● Varia ○ Non so	La tecnica (Resuscitative endovascular balloon for the occlusion of the aorta) REBOA rappresenta una nuova frontiera per il trattamento delle emorragie interne non comprimibili. Lo shock emorragico non controllabile rappresenta il fattore primario per la mortalità precoce nel paziente vittima di un trauma. È in questo contesto che si inserisce la tecnica REBOA, che consiste nel gonfiaggio di un palloncino all'interno dell'aorta in grado di arrestare l'emorragia per dare maggior tempo all'équipe chirurgica per ottenere l'emostasi. Il REBOA è una tecnica temporanea, invasiva, per l'arresto o la riduzione della perdita ematica sino al controllo definitivo dell'emorragia mediante procedura endovascolare o intervento chirurgico (Cannon et al. 2018). Nel setting pre-ospedaliero il REBOA è l'unico strumento in grado di tener sotto controllo efficacemente le emorragie non comprimibili, per il tempo della gestione sulla scena e durante il trasporto in Ospedale (Thabouillot et al. 2018). L'applicazione del REBOA è indicato nei pazienti con: - imminente arresto cardiaco traumatico per verosimile causa emorragica, applicato solitamente in zona 1, con un tempo mediano di gonfiaggio limitato (McGreevy et al. 2019); - severo shock emorragico per lesioni addominali oe/o pelviche (Saito et al. 2015; Fitzgerald et al. 2020); - severa frattura pelvica (Fitzgerald et al. 2020), dove uno studio case-series ha dimostrato che l'applicazione nel setting pre-ospedaliero del REBOA in zona III ha migliorato la sopravvivenza rispetto all'intervento ritardato in pronto soccorso (Lendrum et al.); - trauma penetrante toracico, secondo un algoritmo proposto in uno studio di Ordoñez del 2020 (Ordonez Carlos et al. 2020). Sito di gonfiaggio del REBOA: Al fine di individuare l'idoneo sito di gonfiaggio del palloncino è bene tenere in considerazione che l'aorta può essere suddivisa in tre zone: ZONA 1: Situata tra l'arteria succlavia sinistra (termine dell'arco aortico) e il tronco celiaco — Questa zona è il sito target nel trattamento dell'emorragia sottodiaframmatica e comunque qualora non si sia riusciti ad individuare l'origine del sanguinamento in modo tale da avere la certezza che il clampaggio sia craniale rispetto al sito emorragico. ZONA 2: Situata tra tronco celiaco e arteria renale piu' caudale — Questa zona rappresenta l'unica dove è controindicato il gonfiaggio del palloncino in quanto in questa sede originano i tronchi splancnici e il posizionamento in urgenza non consente un controllo preciso della sede del pallone e quindi dei vasi esclusi dal flusso ZONA 3: Situata tra arteria renale più caudale e biforcazione aortica nelle arterie iliache comuni — Questa zona rappresenta il target dove gonfiare il palloncino nel caso in cui si sospetti un'emorragia pelvica Il REBOA si impiega in ZONA 1 e ZONA 3, mai ZONA 2. La FAST (Focused Assessment with Sonography in Trauma) può fornire l'indicazione della zona in cui cuffiare il palloncino: FAST positiva: indica la presenza di un'emorragia endoaddominale, motivo per cui il palloncino deve essere cuffiato in Zona 1; FAST negativa: e presenza di evidenze radiografiche di frattura del bacino (eseguibile a letto del paziente mediante apparecchio trasportabile) possono indicare un sanguinamento pelvico, per cui il gonfiaggio deve avvenire in Zona 3; FAST incerta: nel caso in cui la FAST non escluda con certezza la presenza di liquido libero endoaddominale e il paziente sia instabile da un punto di vista emodinamico il palloncino va comunque cuffiato in Zona 1.	



Il gonfiaggio del REBOA in zona 1 è piu'efficace per alzare la pressione (per non più di 15-20 minuti), mentre il gonfiaggio in zona 3 (per non più di 30 minuti) è meno efficiente sulla pressione ma determina meno effetti collaterali in quanto causa ischemia solo degli arti inferiori e non del distretto splancnico

Effetti desiderabili

Quanto considerevoli sono gli effetti desiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Irrilevanti ○ Piccoli ○ Moderati ○ Grandi ● Variano ○ Non so	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono stati individuati 324 records. Sono state trovate 5 revisioni sistematiche di studi osservazionali e 10 studi osservazionali che soddisfano i criteri di eleggibilità. Nessuno studio randomizzato controllato. Un protocollo di trial registrato ma sospeso. In seguito alla valutazione dell'overlapping tra studi inclusi nelle revisioni sistematiche e gli studi derivanti dalla search strategy, 11 studi primari osservazionali sono stati inclusi (Abe et al. 2016; Aso et al. 2017; Brenner et al. 2018; DuBose et al. 2016; Garcia Alberto et al. 2020; Inoue et al. 2016; Joseph et al. 2019; Matsumura et al. 2018; Moore et al. 2015; Yamamoto et al. 2019; Norii, Crandall, and Terasaka 2015). (**Appendice B; Appendice C; Appendice F**) I risultati includono 3 comparazioni: - 5 studi comparano REBOA verso Restuscitative Thoracotomy (RT); - 1 studio compara REBOA verso Restuscitative Thoracotomy + REBOA;	Gli studi esaminati non hanno utilizzato dei criteri di valutazione sugli esiti a distanza che consentano un giudizio conclusivo da parte del panel.

- 5 studi comparano REBOA verso no-REBOA.

Gli effetti desiderabili considerevoli sono indicati in **Appendice C** e riassunti di seguito:

Critici

1. Mortalità a 24 ore, 30 giorni/1 mese

In totale, 11 studi riportano dati sulla mortalità. Tuttavia, nove non definisco il time-frame a cui viene raccolto il dato, definendo la mortalità "overall o at discharge".

- Quattro studi riportano dati sulla mortalità a 24 ore.
- Cinque studi riportano la mortalità in ED
- Tre studi riportano dati a 1 mese

In **Appendice C** sono riportate le analisi quantitative crude e aggiustate della mortalità in-hospital degli studi (tabella 2), nello specifico:

- **Figura 1, tabella 2**. Meta-analisi con stime crude per overall mortality.
- **Figura 2, tabella 2**. Meta-analisi con stime aggiustate per overall mortality.
- **Figura 3, tabella 3**. Meta-analisi con stime aggiustate per mortalità in emergency department.
- **Figura 4, tabella 4.** Meta-analisi con stime aggiustate per mortalità a 24 ore .
- **Figura 5, tabella 5**. Meta-analisi con stime aggiustate per mortalità a un mese.

In Appendice C, figura 2 analisi di sensibilità per spiegare il comportamento dell'eterogeneità trovata in figura 1, escludendo studi che disperdevano l'effetto.

2. Volume degli emocomponenti

In totale, sei studi riportano l'outcome di interesse (Joseph 2019; Garcia 2020; Brenner 2018; Aso 2016; Dubose 2016; Yamamoto 2019). Quattro studi (Brenner 2018; Dubose 2016; Garcia 2020; Joseph 2019) riportano valori in mediana (range interquartile). Uno studio, Aso 2016, riporta l'outcome in termini di quantità totale di trasfusione entro 1 giorno dall'ammissione in ED. Mentre, uno studio, Yamamoto 2019, riporta l'outcome in numero di pazienti. Vedi tabella (**Appendice C, tabella 6**) sottostante:

Autore	Outcome	Units	REBOA	Control non-REBOA	p value
cryoprecipitate					
Dubose 2016	cryoprecipitate 24 h	median (IQR)	1(11)	0(1)	0,14
Garcia 2020	cryoprecipitate 6h	median (IQR)	6.5(0-10)	0(0-0)	0,21
crystalloids					
Garcia 2020	crystalloids 24 h mliters	median (IQR)	4649(3290-6329)	4420(2705-6350)	0,13
Dubose 2016	crystalloids- liters 24 h liters	median (IQR)	4(5)	3(5)	0,12
plasma					
Joseph 2019	plasma 24h	median (IQR)	9(6-20)	10(7-20)	0,17
Brenner	plasma 24h	median (IQR)	9 (16)	4 (9)	0,11
Dubose 2016	plasma 24h	median (IQR)	14.5(18)	6(18)	<0.001
Joseph 2019	plasma 4h	median (IQR)	3 (2-5)	3(2-6)	0,001
Garcia 2020	plasma 6h	median (IQR)	4(2.5-6)	0(0-4)	<0.001
platelets					
Joseph 2019	platelets 24h	median (IQR)	7(3-13)	8(3-12)	<0.001
Dubose 2016	platelets 24h	median (IQR)	5.5(12)	1.5(11)	0,5
Joseph 2019	platelets 4h	median (IQR)	4(3-9)	4(3-8)	0,05
Garcia 2020	platelets 6h	median (IQR)	0.5(0-6)	0(0-0)	0,05
PRBCs					

Joseph 2019	PRBCs 24 h	median (IQR)	9(5-20)	10(4-21)	0,3988
Brenner	PRBCs 24 h	median (IQR)	10 (21)	7.8 (10)	0,654
Dubose 2016	PRBCs 24 h	median (IQR)	20.5(18)	13.5(18)	0,343
Joseph 2019	PRBCs 4 h	median (IQR)	6 (3-8)	7(3-9)	0,872
Garcia 2020	PRBCs 6 h	median (IQR)	5(3-9)	2(0-4)	0,149
Total amount of transfusion					
Aso 2016	Total amount of transfusion within 1 d after admission: average (SD), mL	media (sd)	2.396 (1.872)	2.820 (2.782)	0,697
Trasfusion in number of patients					
Abe 2016	trasfusion in number of patients	n (%)	542 (85%)	197(74%)	0,001
Yamamoto 2019	trasfusion in number of patients	n (%)	111(95%)	113 (97%)	<0,001

3. Qualità della vita correlata alla salute (ad es. Discharge Glasgow Coma Scale)

Quattro studi hanno riportato l'outcome di interesse (Brenner 2018; Dubose 2016; Joseph 2019; Nori 2015).
L'outcome Discharge Glasgow Coma Scale fra i sopravvissuti, come proxy della qualità di vita, è stato riportato da quattro studi (DuBose 2016, Brenner 2018, Nori 2015, Joseph 2019).
In Dubose 2016 nessuna differenza significativa è stata trovata fra i due gruppi in (mediana REBOA 15 and mediana Control 15, p=0.766). Brenner 2018 riporta dati inerenti Discharge Glasgow Coma Scale fra i sopravvissuti solo per la coorte pre-hospital trovando una differenza statasticamente significativa (mediana REBOA 9 and mediana Control 3, p=0.026).
Nori 2015 e Joseph 2019 riportano i dati delle sottoanalisi dei soli pazienti che hanno ricevuto il REBOA. In Nori 2015 i pazienti che sopravvivono hanno una scala Glasgow Coma Scale (GCS) significativamente più alta rispetto a chi non sopravvive (media GCS, 11.6 vs. 7.2; p =0.0001) così come Joseph 2019 (p=0.04).

5. Controllo dell'emorragia in emergenza

Uno studio, Jospeh et al. 2019, riporta il tempo di controllo dell'emorragia rispetto all'intervento. Si riportano i risultati nella tabella sottostante (**Appendice C, tabella 12**)

Variable	Patients, No. (%)		*P* Value
	No-REBOA Group (n = 280)	REBOA Group (n = 140)	
Hemorrhage control intervention			
Angioembolization	85 (30.4)	40 (28.6)	.18
Time to angioembolization, median (IQR), min	46 (31-69)	59 (39-78)	.04
Laparotomy	190 (67.9)	96 (68.6)	.33
Time to laparotomy, median (IQR), min	33 (26-62)	45 (35-69)	.04

Inoltre, Matsumara et al 2017 riporta il tempo di controllo dell'emorragia dall'arrivo alla scena (**Appendice C, tabella 13**).

Characteristics and outcomes	REBOA alone ($N=76$)	RT + REBOA ($N=30$)	P
Time course (min)			
Arrival to REBOA	60 (27–85)	32 (20–63)	0.026
Arrival to definitive care	71 (50–101)	25 (11–60)	<0.001

Gli stessi autori riportano in discussione: "The shorter arrival to access time and lower ISS were significantly associated with increased survival in hemorrhagic patients undergoing REBOA. Patients with arterial access obtained within 21.5 minutes from arrival demonstrated prompt subsequent hemostasis and better survival curves. Proactive early access in the resuscitation phase may be associated with survival outcomes."

Importanti:

1. Mortalità a 12 mesi

Nessuno studio riporta la mortalità a 12 mesi.

2. Miglioramento dell'emodinamica (pressione sanguigna e frequenza cardiaca)

Due studi riportano l'outcome di interesse (Brenner 2016, Dubose 2016), di seguito si riporta la tabella descrittiva (**Appendice C, tabella 14**):

	REBOA (n=46)	**Control (n=68)**	**P value**
Dubose 2016			
Improvement in hemodynamics with aortic occlusion, n (%)	29(67.4%)	42(61.8%)	0.544
Hemodynamic stability (SBP consistently above 90 mm Hg) achieved with aortic occlusion, n (%)	22 (51.2%)	19(27.9%)	0.014
Hemodynamic improved with 2ndaortic occlusion, n (%)	2/2 (100%)	7/9 (77.8%)	0.244
Hemodynamic stability (SBP consistently > 90 mm Hg) achieved with 2nd aortic occlusion, n (%)	2/2 (100%)	6/9 (66.7%)	0.217
Brenner 2016			
Post-occlusion SBP (mean/sd) mmHg	89 (65)	30 (51)	P<0.001
Duration of aortic occlusion, min, median IQR	31 (57)	19 (21)	0.002

Effetti indesiderabili

Quanto considerevoli sono gli effetti indesiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Grandi ● Moderati ○ Piccoli ○ Irrilevanti ○ Variano ○ Non so	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono stati individuati 324 records. Sono state trovate 5 revisioni sistematiche di studi osservazionali e 10 studi osservazionali che soddisfano i criteri di eleggibilità. Nessuno studio randomizzato controllato. Un protocollo di trial registrato ma sospeso. In seguito alla valutazione dell'overlapping tra studi inclusi nelle revisioni sistematiche e gli studi derivanti dalla search strategy, 11 studi primari osservazionali sono stati inclusi. (**Appendice B; Appendice C**)	

Gli effetti indesiderabili considerevoli (**Appendice C**):

Critici:

4. Eventi avversi

Tre studi riportano eventi avversi per entrambi i gruppi a confronto (REBOA vs controllo) (Joseph 2019; Dubose 2016; Brenner 2018). Mentre, uno studio (Garcia 2020) riporta dati di eventi avversi solo per il gruppo REBOA.

In Appendice C sono riportate le tabelle descrittive relative agli studi citati **(Appendice C, tabella 7, 8 , 9 e 10,11).**

Le complicazioni da REBOA più frequenti sono amputazioni,ematoma e pseudoaneurisma (**Appendice C, tabella 7**), di seguito riportata:

	REBOA	*Control*	*p-value*
Need of amputation			
Brenner 2018	*1 (1.2%)*	-	
DuBose 2016	*0 (0%)*	-	
Joseph 2019	*5 (3.6%)*	*2 (0.7%)*	*0.04*
Hematoma			
Brenner 2018	*0 (0%)*	-	
DuBose 2016	*0 (0%)*	-	
Pseudoaneurism			
Brenner 2018	*0 (0%)*		
DuBose 2016	*1 (2.2%)*		

Importanti:

3. Fallimento della tecnica REBOA

Questo outcome è presente in due studi che riportano il numero di soggetti in cui la tecnica è stata eseguita con successo. (**Appendice C, tabella 15**).

Successful aortic occlusion	**REBOA n (%)**
Brenner 2018	78/83 (94)
Dubose 2016	42/46 (91.3)

Qualità delle prove

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
● Molto bassa ○ Bassa ○ Moderata ○ Alta ○ Nessuno studio incluso	La qualità delle prove è molto bassa (**Appendice E**).	

Valori

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
● Importante incertezza o variabilità ○ Possibile importante incertezza o variabilità ○ Probabilmente nessuna incertezza o variabilità importante ○ Nessuna incertezza o variabilità importante	E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 0 records.	Il panel non ritiene di avere gli elementi per esprimere giudizi conclusivi.

Bilancio degli effetti

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ È in favore del confronto ○ Probabilmente è in favore del confronto ○ Non è in favore né dell'intervento né del confronto ○ Probabilmente è in favore dell'intervento ○ È in favore dell'intervento ● Varia ○ Non lo so	Il bilancio tra effetti desiderabili e indesiderabili è da valutare a seconda delle indicazioni per il trattamento REBOA. Alcuni studi riportano la comparazione tra REBOA e open aortic occlusion in corso di resuscitative thoracotomy. Altri confrontano REBOA con non REBOA nelle emorragie addomino-pelviche. Inoltre, molti studi inclusi non hanno un vero gruppo di controllo (alcuni studi considerano controllo pazienti che non sono stati sottoposti a REBOA e/o toracotomia).	È stata differenziata la letteratura che considera come confronto il non utilizzo del REBOA da quella che considera la toracotomia resuscitativa. Nel primo caso non si sono osservati dei risultati a favore dell'intervento. Nel secondo caso la metanalisi suggerisce una riduzione della mortalità. La tipologia di pazienti è verosimilmente diversa: nel caso del non REBOA come comparatore si tratta di pazienti ipotesi con gravità variabile; nel caso della toracotomia resuscitativa si tratta di pazienti in peri o arresto cardiaco post-traumatico.

Risorse necessarie

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
● Costi elevati ○ Costi moderati ○ Costi e risparmi irrilevanti ○ Risparmi moderati ○ Risparmi elevati ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 3 record relativi alla costo-efficacia della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero. È stata inclusa una revisione per rispondere al dominio considerato (Renna Maxwell et al. 2019). Tale revisione calcola i costi utilizzando le tariffe del National Health Service (UK) e li integra con dati disponibili della letteratura: confronta i costi del REBOA con i costi della toracotomia resuscitativa (RT). La resuscitative thoracotomy richiede strumenti meno costosi rispetto al REBOA il cui costo del kit è di £1000.	Nel contesto italiano i costi variano da 1500 a 2500 euro per catetere.

Qualità delle prove relative alle risorse necessarie

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Molto bassa ○ Bassa ○ Moderata ● Alta ○ Nessuno studio incluso	Le prove relative alle risorse necessarie sono contestualizzate in Inghilterra e nel contesto internazionale. Essendo il contesto inglese differente dal contesto italiano in termini di sistema sanitario nazionale, disponibilità di risorse economiche, la qualità delle prove risente di una non diretta trasferibilità (indirectness), perciò con limitata applicabilità al contesto italiano.	Nel contesto italiano i costi variano da 1500 a 2500 euro per catetere.

Costo-efficacia

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ È in favore del confronto ○ Probabilmente è in favore del confronto ● Non è in favore né del confronto né dell'intervento ○ Probabilmente è in favore dell'intervento ○ È in favore dell'intervento ○ Varia ○ Nessuno studio incluso	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare un solo studio relativo al costo-efficacia della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero. È stata inclusa una revisione per rispondere al dominio considerato (Renna Maxwell et al. 2019). Tale revisione calcola i costi utilizzando le tariffe del National Health Service (UK) e li integra con dati disponibili della letteratura: confronta i costi del REBOA con i costi della toracotomia RT (resuscitative thoracotomy). Sono stati inclusi 12 studi per valutare l'intervento REBOA e 20 studi per valutare la Toracotomia Resuscitativa. Il rapporto incrementale della costo-efficacia del REBOA quando comparato a RT è di £44,617.44 per anni di vita aggiustati per qualità di vita. Il rapporto incrementale della analisi costo-efficacia, che eccede la soglia di £ 30,000/ per anni di vita aggiustati per qualità di vita che il National Institute for Health and Clinical Effectiveness sono disposti a pagare, suggerisce che l'intervento non è costo efficace rispetto al RT. Comunque, gli autori riportano che il REBOA guadagna il 157% di miglioramento in utilità a fronte di un lieve incremento di costi del 31.5%. Sebbene il REBOA è stato definito dagli autori della revisione come no-cost-efficient quando comparato a RT, l'esperienza clinica e le capacità dei professionisti sanitari dovrebbero guidare nella scelta su quale intervento prioritizzare per il paziente traumatizzato nel contesto di emergenza.	Non sono disponibili dati sufficienti per fare un'analisi costo-efficacia.

Equità

Quale sarebbe l'impatto in termini di equità?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Riduce l'equità ○ Probabilmente riduce l'equità ● Probabilmente nessun impatto ○ Probabilmente	Non sono stati identificati studi relativi al contesto internazionale e italiano.	

migliora l'equità ○ Migliora l'equità ○ Varia ○ Non so		

Accettabilità

L'intervento è accettabile per i principali stakeholders?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ○ Probabilmente si ○ Si ● **Varia** ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 103 records relativi all'accetta bilità/fattibilità della gestione del REBOA setting pre-ospedaliero. Uno studio risponde al quesito dell'accettabilità (Jarvis et al. 2019): è stato identificato uno studio cross sectional che ha sottoposto un questionario a 158 direttori di trauma center con lo scopo di valutare il tasso di utilizzo del REBOA, le indicazioni e la sequenza di trattamento per soggetti emodinamicamente instabili con fratture pelviche e il consenso nell'utilizzo di questa tecnica. Lo studio è stato effettuato tra i trauma centers American College of Surgeons-verified Level I. Di seguito le tabelle relative al questionario e alle risposte.	

Survey Question	Responses	% (n)	n
Does your hospital use a REBOA to treat hemodynamically unstable pelvic fractures?	Yes	42% (15)	36
	No	58% (21)	
What indicates a patient with a pelvic fracture for REBOA?	HDU	50% (7)	14
	HDU & IR is unavailable	14% (2)	
	HDU & negative FAST	7% (1)	
	HDU & not a candidate for angioembolization	29% (4)	
In what order are the following treatments utilized for hemodynamically unstable pelvic fractures? REBOA, angioembolization, and pelvic packing	Angioembolization, PP, REBOA	33% (5/15)	15
	Angioembolization, REBOA, PP	13% (2/15)	
	PP, Angioembolization, REBOA	13% (2/15)	
	REBOA, Angioembolization, PP	20% (3/15)	
	REBOA, PP, Angioembolization	20% (3/15)	
Of those who said hemodynamic instability was the only indicator, what was the order of treatment? REBOA, angioembolization and pelvic packing	PP, Angioembolization, REBOA	33% (2/6)	6
	Angioembolization, PP, REBOA	33% (2/6)	
	Angioembolization, REBOA, PP	17% (1/6)	
	REBOA, Angioembolization, PP	17% (1/6)	

REBOA resuscitative endovascular balloon occlusion of the aorta, *HDU* hemodynamically unstable, *IR* interventional radiology, *FAST* focused assessment of sonography in trauma, *PP* pelvic packing.

	Does Not Use REBOA $n = 21$	Uses REBOA $n = 15$	n	p
Does your hospital have a guideline for the management of pelvic fractures?				
No	33% (7)	13% (2)	36	0.25
Yes	67% (14)	87% (13)		
In what year was your guideline for the management of pelvic fractures implemented?				
2005	11% (1)	0	18	0.55
2006	11% (1)	0		
2011	0	11% (1)		
2013	11% (1)	22% (2)		
2014	11% (1)	0		
2015	22% (2)	11% (1)		
2016	22% (2)	56% (5)		
2017	11% (1)	0		
What published guideline does your hospital follow?				
ATLS	18% (2)	0	21	0.17
EAST	36% (4)	50% (5)		
TQIP	0	30% (3)		
WTA	36% (4)	20% (2)		
Other[a]	9% (1)	0		
How long has your trauma center been a Level I trauma center?				
≤ 1 year	5% (1)	7% (1)	36	0.94
> 1 year to 2 years	19% (4)	7% (1)		
> 2 years to 5 years	19% (4)	20% (3)		
> 5 to 10 years	5% (1)	7% (1)		
> 10 years	52% (11)	60% (9)		
How many trauma admissions did your site have in 2017?				
Low volume (≤ 1500)	14% (3)	7% (1)	36	0.63
High volume (> 1500)	86% (18)	93% (14)		

ATLS Advanced Trauma Life Support, *EAST* Eastern Association for The Surgery of Trauma, *TQIP* Trauma Quality Improvement Project, *WTA* Western Trauma Association. [a] Participant indicated that protocol is based on the Orthopedic Trauma Association, *EAST*, *TQIP* and a literature review

Fattibilità

È fattibile l'implementazione dell'intervento?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ● Probabilmente sì ○ Si ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 103 records relativi all'accettabilità/fattibilità della gestione del REBOA nel setting pre-ospedaliero. Nove studi rispondono al quesito della fattibilità. **Applicability/time/complications (paraplegia)** Inoltre, l'applicabilità/efficacia e successo del REBOA deve considerare il rapporto rischi benefici in relazione al tempo: in generale, l'aortic cross-clamping ha un alto rischio di paraplegia se il tempo di cross-clamping si estende oltre i 30 minuti (von Oppell et al. 1994). Saito et al (Saito et al. 2015) descrivono 19 casi in cui, la durata mediana dell'aortic occlusion era più breve nei sopravvissuti che nei morti (21 minuti vs. 35 minuti, p = 0.05). Un altro studio, Fabian et al. 1997 (Fabian et al. 1997) ha evidenziato che un aortic cross clamp chirurgico oltre i 30 minuti è associato a rischio elevato di paraplegia; la associazione di bypass temporaneo tra ventricolo sinistro e aorta toracica distale produce eventi di paraplegia in tasso inferiore rispetto al clamp senza shunt. La tabella di seguito illustra gli effetti di un tempo minore o maggiore a 30 minuti del clamp: Group | Paraplegia | No Paraplegia | *p* Value Clamp and sew | 43.9 ± 12.2 | 29.2 ± 11.0 | 0.003 Bypass | 51.2 ± 17.4 | 44.0 ± 24.9 | 0.49 [a] Excludes patients with unrecorded cross clamp times. Infine Lo Statement pubblicato nel 2019 dall' American College of Surgeons Committee on Trauma, the American College of Emergency Physicians, the National Association of Emergency Medical Services Physicians and the National Association of Emergency Medical Technicians dall'American Society riporta la seguente indicazione: "Zone 1 REBOA should not be used if patients cannot proceed expeditiously to a definitive hemorrhage control procedure within 15min. Total aortic occlusion times greater than 30min are associated with increased ischemic complications and risk of mortality."; "Zone 3 REBOA may be tolerated for longer periods of time and may be used as an adjunct to management of pelvic fracture bleeding including angioembolization and/or pelvic packing, and/or stabilization. Once Zone 3 occlusion has been performed, patients should proceed expeditiously to definitive hemorrhage control. Although the maximum acceptable occlusion time for Zone 3 is unknown, the system should target less than 30min, but no greater than 60min of total occlusion time." (Bulger et al. 2019) Nessuno studio ha sistematizzato l'utilizzo dell'occlusione parziale. Diversi case reports indicano la possibilita' di prolungare I tempi di ischemia sia in zona 1 che in zona 3 utilizzando questa tecnica ma al momento non è disponibile alcuna evidenza. **Setting** L'inserzione del REBOA viene applicata più frequentemente nel pronto soccorso, o in sala operatoria (Bekdache et al. 2019; Gamberini et al. 2017), in quanto la pratica sulla scena o durante il trasporto deve essere effettuata con cautela ed in casi selezionati per i quali si deve avere un programma successivo di controllo definitivo dell'emorragia ben definito (Bekdache et al. 2019). Nelle aree rurali, quando il tempo di trasporto al trauma centre è elevato, è consigliato il posizionamento del REBOA nella zona III solo se l'emorragia è esclusivamente pelvica o giunzionale, in quanto il tempo di occlusione completa può essere prolungato (Thabouillot et al. 2018). **Training/skills/expertise** Il REBOA dovrebbe essere applicato da chirurghi generali o vascolari, anestesisti, medici d'urgenza, radiologi interventisti ~~e~~ che sono responsabili del controllo dell'emorragia in emergenza qualificati nella procedura. Il REBOA viene scelto come procedura nel paziente in extremis da medici che non sono in grado di effettuare la toracotomia (Thabouillot et al. 2018), e in generale, gli operatori che inseriscono il REBOA variano a seconda del contesto (Gamberini et al. 2017), (Bekdache et al. 2019). Le abilità possono essere facilmente acquisite anche dai medici con limitate capacità endovascolari, grazie all'opportunità di frequentare corsi sulle procedure di emergenza. Pare, infatti, che l'inserzione di 3-5 REBOA sotto la supervisione di un esperto, o un periodo di training di alcuni mesi, potrebbero essere sufficienti per assimilare le competenze necessarie (Marciniuk et al. 2019). Tuttavia, non esiste una certificazione universale per il corretto posizionamento del REBOA (Gamberini et al. 2017). Ad ogni modo, un approccio multidisciplinare è necessario per implementare REBOA nell'emergenza. Tutti i membri del gruppo multidisciplinare dovrebbero essere familiari con lo strumento così da garantire la continuità terapeutica dall'emergenza alla terapia intensiva (Zakaluzny et al. 2019). **Experience in children**	È richiesto un addestramento specifico.

	Ad oggi, nei bambini, la pratica del REBOA risulta poco conosciuta a causa della mancanza di i) evidenze di alta qualità, ii) equipaggiamento, iii) esperienza dei medici e la possibilità di complicazioni, quali le lesioni vascolari, durante la procedura. Per questi motivi, nei bambini la tecnica del REBOA dovrebbe essere utilizzata con ancora più attenzione (Campagna Giovanni et al. 2020).	

RIASSUNTO DEI GIUDIZI

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

TIPO DI RACCOMANDAZIONE

N. 12

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

N. 13

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

CONCLUSIONI

Raccomandazione

N 12. Nel paziente con Trauma Maggiore e con ipotensione da shock emorragico non vi è indicazione all'utilizzo del REBOA se non nell'ambito di adeguati programmi di sperimentazione [raccomandazione forte, qualità delle prove molto bassa].

N 13. In pazienti in arresto/peri-arresto cardiocircolatorio da cause presumibilmente emorragiche è preferibile l'utilizzo del REBOA alla toracotomia resuscitativa [raccomandazione condizionata, qualità delle prove molto bassa].[1]

Giustificazione

L'eterogeneità delle evidenze nei due sottogruppi (pazienti in periarresto vs paz con ipotensione/shock) suggerisce due raccomandazioni distinte. In particolare non vi sono evidenze a supporto dell'utilizzo del REBOA se non in condizioni di estrema gravità. Al contrario il suo utilizzo in condizioni meno critiche configura dei rischi consistenti in assenza di vantaggi dimostrati: in queste condizioni è necessaria una adeguata sperimentazione clinica.

[1] Nel corso del meeting del 9 settembre 2020 il panel, preso atto dei commenti degli stakeholder, ha ritenuto di dover modificare la raccomandazione come riportato a pagina 3 del presente documento.

Considerazioni relative ai sottogruppi

Si ribadisce il duplice risultato dell'analisi della letteratura nei pazienti da ipotensione da emorragia e nei pazienti con arresto/peri-arresto che giustifica la formulazione delle due differenti raccomandazioni.

Considerazioni per l'implementazione

Subordinata all'acquisizione di prove di efficacia. Necessaria inoltre l'acquisizione di uno skill specifico da parte degli operatori.

Monitoraggio e valutazione

Studi controllati nell'ambito di strutture di ricerca qualificate.

Priorità della ricerca

Campo prioritario per la ricerca.

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Appendice A - Quesito clinico e strategia di ricerca

CQ7: Controllo dell'emorragia nel setting pre- e intraospedaliero: REBOA

CQ 7. Review question: Is Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) clinically and cost effective in in the Management of major exsanguination in trauma?

Objective: To determine the clinical and cost effectiveness of Resuscitative Endovascular Balloon Occlusion of the Aorta clinically in the Management of major exsanguination in trauma	
Population	Children, young people and adults TRAUMA victims in pre-hospital, emergency department (ED) and operating room (OR) during resuscitation phase - (terms to be probably included in population: trauma, hemorrhage control, hemorrhage, resuscitation, shock, , occlusion of the aorta, critical hemorrhage of the abdomen, critical hemorrhage of the pelvis, abdomino-pelvic hemorrhage")
Intervention	**REBOA – Resuscitative Endovascular Balloon Occlusion** (terms: "aortic balloon occlusion", "aortic balloon tamponade", "REBOA", "Resuscitative Endovascular Balloon Occlusion" or ABO or "aortic balloon")
Comparison	Resuscitative Thoracotomy (RT)/ No REBOA
Outcomes	Critical: 1. Mortality at 24 hours, 30 days/1month 2. Volume of blood components 3. Health related quality of life 4. Adverse effects (unnecessary imaging) 5. Time of haemorrhage control Important: 1. Mortality at 12 months 2. Improvement in haemodynamics (bloodpressure and heart rate) 3. Failure/Success of REBOA technique
Exclusion	People with a major trauma resulting from burns
Search strategy	Databases: Medline, Embase, the Cochrane Library Date: No restriction Language: Restrict to English, Italian, Spanish, French, German Study designs: RCTs or Systematic reviews of RCTs; cohorts. CASE REPORT??
The review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed the Newcastle-Ottawa Scale for observational studies, the Cochrane risk of bias tool for RCTs and GRADE.
Analysis	Stratify by age: children (0-17 years), adults (18 and over) Sub-groups if between-study heterogeneity exists: Subgroup children by: neonate (<28 days), infant (to 1 year), child (1-15 years), young people(16-17 years) Sub-group by: Within-study confounders (if cohorts used) Age Injury severity

SEARCH STRATEGIES _CLINICAL QUESTION CQ5

Standard major trauma population

Medline search

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
3.	((serious* or severe* or major) near/3 (accident* or injur* or fall*)):ti
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
11.	(mvas or mva or rtas or rta):ti
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
13.	{or #1-#12}

CRD search terms

1.	MeSH descriptor multiple trauma
2.	MeSH descriptor wounds, gunshot
3.	MeSH descriptor wounds, stab
4.	MeSH descriptor accidents, traffic
5.	MeSH descriptor accidental falls
6.	MeSH descriptor blast injuries
7.	MeSH descriptor accidents, aviation
8.	((trauma* or polytrauma*))
9.	(((serious* or severe* or major or life threaten*) near3 (accident* or injur* or fall*)))
10.	(((mvas or mva or rtas or rta)))
11.	(((stabbed or stabbing or stab or gunshot* or gun or gunfire or firearm* or bullet* or knife* or knives or dagger)))
12.	((((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike*) near3 (accident* or crash* or collision* or smash*))))
13.	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)

Haemorrhagic shock / population

1.	Shock, hemorrhagic/ct
2.	Hemorrhagic shock/ct
3.	Hemorrhagic(a) shock/ti,ab
4.	Haemorrhagic(a) shock/ti,ab
5.	Traumat?(a)shock/ti,ab
6.	Hemorrhage(l)prevention & control/ct
7.	Hemorrhage+nt/ct
8.	Hemorrhage#/ti,ab or haemorrhage#/ti,ab or bleed?/ti,ab
9.	Damage# control#/ti,ab

10.	Exsanguination/ct or exsanguinat?/ti,ab
11.	Shock+nt/ct
12.	Hypovolemia/ct or hypovol!em?/ti,ab
13.	Hypoperfus?/ti,ab
14.	Bloodloss/ti,ab or blood(3w)loss/ti,ab
15.	Olig!em?/ti,ab

INTERVENTION

1.	Resuscitation+nt/ct and balloon occlusion/bi and aorta+nt/ct
2.	Resuscitat?/ti,ab and balloon#/ti,ab and occlusi?/ti,ab and
3.	Aorta/ti,ab
4.	Resuscitat?/ti,ab and endovascular/ti,ab and balloon#/ti,ab
5.	And OCCLUSI?/ti,ab
6.	Open repair/ti,ab
7.	Reboa/ti,ab
8.	Angioplasty balloon#/bi and aorta/bi
9.	Aort? And balloon# and occlusi?/ti,ab
10.	Aort? And balloon# and tampona?/ti,ab

Excluded study designs and publication types
The following study designs and publication types were removed from retrieved results using **the NOT** operator.
Aggiungere alla search con operatore NOT I seguenti search terms:

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9	animals/ not humans/
10.	exp animals, laboratory/
11	exp animal experimentation/
12	exp models, animal/
13	exp rodentia/
14	(rat or rats or mouse or mice).ti.
15	or/1-14

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	animal/ not human/
7.	nonhuman/
8.	exp animal experiment/
9.	exp experimental animal/
10.	animal model/
11.	exp rodent/
12.	(rat or rats or mouse or mice).ti.
13.	or/1-12

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

CQ7: Controllo dell'emorragia nel setting pre- e intraospedaliero: REBOA

Caratteristiche degli studi inclusi

Study	**Abe 2016**
Study type	Retrospective cohort study
Number of studies/ number of participants	903 trauma patients
Countries and Settings	Nationwide trauma registry in Japan
Funding	supported by JSPS KAKENHI JP 16 K15388 and Ministry of Health, Labour and Welfare
Duration of study	Between 2004 and 2013
Age, gender, ethnicity	Mean age was 53.7 ± 21.2 years; 611/903 (67.7%) male. REBOA: mean age 52.5 ± 21.2 years; 417/636 (66%) male; ACC: mean age 56.7 ± 21.1 years; 417/636 (66%) male
Patient characteristics	Presence of critical trauma and reception of either REBOA or ACC.
Intervention	REBOA (n=636) Resuscitative open aortic cross-clamping (ACC) (n=267)
Outcomes	- in-hospital mortality - ED mortality - Blood transfusion

Study	**Aso 2017**
Study type	Retrospective cohort study
Number of studies/ number of participants	259 trauma patients
Countries and Settings	Japanese Diagnosis Procedure Combination database
Funding	Grants for Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare, Japan
Duration of study	From July 1, 2010, to March 31, 2014.
Age, gender, ethnicity	REBOA:male 114 (59.7%); RT: male 44 (64.7%)
Patient characteristics	Trauma patients with uncontrolled hemorrhagic shock (n = 259) excluded penetrating thoracic injuries aged 15 years or older who received REBOA or RT within 1 day after admission.
Intervention	REBOA (n=191) Resuscitative thoracotomy (n=68)
Outcomes	- in-hospital mortality - ventilator-free days (VFDs) - intensive care unit (ICU)-free days - total amount of fluid infusion within 1 day after admission (mL) - total amount of transfusion within 1 day after admission (mL) - total hospitalization costs

Study	**Brenner 2018**
Study type	Prospective cohort study
Number of studies/ number of participants	285 trauma patients
Countries and Settings	Approved by the American Association for the Surgery
Funding	Not reported
Duration of study	From November 2013 to January 2017
Age, gender, ethnicity	REBOA: mean age 44.6 ± 20.2; male 65 (78.3%); RT: mean age 37.8 ± 15.7; male 168 (83.2%)
Patient characteristics	Adult trauma and acute care surgery (age ≥ 18) patients undergoing aortic occlusion (AO) in the acute phases after injury
Intervention	REBOA (n = 83); Resuscitative thoracotomy (n=202)
Outcomes	- in-hospital mortality - Complication - Units packed red blood cells - Units fresh frozen plasma - Health related quality of life - (neurologic outcomes: Glasgow Coma Outcomes Score)

Study	**DuBose 2016**
Study type	Prospective cohort study
Number of studies/ number of participants	114 patients
Countries and Settings	AAST Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) registry prospectively identified trauma patients requiring AO from 8 ACS level I centers
Funding	Not reported
Duration of study	From November 2013 February 2015
Age, gender, ethnicity	Overall, male (80.7%); mean age 40.8 years. REBOA: mean age 43.2 ± 19.6; male 32/46 (69.6%) Open Aortic occlusion: mean age 39.2 ± 16.7; male 60/68 (88.2%)
Patient characteristics	Adult trauma and acute care surgery (age ≥ 18) patients undergoing aortic occlusion (AO) in the acute phases after injury
Intervention	REBOA (n=43) Open Aortic occlusion (AO) (n=68)
Outcomes	- Hemodynamic stability - Improvement in hemodynamicsred blood cell requirements - in hospital mortality - ED mortality - Complications - Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)

Study	**Garcia 2020**
Study type	Retrospective cohort study
Number of studies/ number of participants	345 patients
Countries and Settings	Clinical records of patients with torso trauma who underwent surgical intervention for haemorrhage control at Fundación Valle del Lili (FVL) University hospital in Cali, Colombia
Funding	Not reported
Duration of study	From December 2014 to January 2018.
Age, gender, ethnicity	Overall, males (n = 312, 90.4%); age, median [IQR]: 27 [21–35]) victims of severe penetrating injuries (ISS, median [IQR]: 25 [16–25])
Patient characteristics	Patients with penetrating trauma, requiring emergency surgery
Intervention	REBOA (n=28) No REBOA/Control (n=317)
Outcomes	- in hospital mortality - PRBCsA in first 6 h - PlasmaA in first 6 h - PlateletsA in first 6 h - CryoA in first 6 h - Crystalloids in first 24 h - Thoracic damage control - Abdominal damage control - complications

Study	**Inoue 2016**
Study type	Retrospective cohort study
Number of studies/ number of participants	12053 patients
Countries and Settings	Japan Trauma Data Bank
Funding	Not reported
Duration of study	Unclear
Age, gender, ethnicity	REBOA: age, median IRQ 54 (35–70); male 436 (68.8%) Without REBOA: age, median IRQ 53 (34–69); male 7,771 (68.1%)
Patient characteristics	trauma patients who had undergone emergency surgery or transcatheter embolization on the chest, abdomen, or pelvis.
Intervention	REBOA (n=634) Without REBOA (n=11.419) Propensity score matching selected 625 patients each for the with-REBOA and without-REBOA groups
Outcomes	- in hospital mortality - ED mortality

Study	**Joseph 2015**
Study type	Case-control retrospective study
Number of studies/ number of participants	420 patients
Countries and Settings	American College of Surgeons Trauma Quality Improvement Program data set, a national multi-institutional database of trauma patients in the United States
Funding	Not reported
Duration of study	2015-2016
Age, gender, ethnicity	REBOA: 36 women and 104 men; mean [SD] age, 44 [20] years; No-REBOA: 77 women and 203 men; mean [SD] age, 43 [19] years.
Patient characteristics	all adult patients (≥18 years of age) who received REBOA within 1 hour of presentation to the emergency department (ED)
Intervention	REBOA (n=140) no-REBOA (n=280)
Outcomes	- in hospital mortality - ED mortality - transfusion requirements at 4 hours and 24 hours after injury, - in-hospital complications (deep venous thrombosis, pulmonary embolism, stroke,myocardial infarction, extremity compartment syndrome - Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)

Study	**Moore 2015**
Study type	Retrospective cohort study
Number of studies/ number of participants	96 patients
Countries and Settings	Trauma registry data; Texas, USA
Funding	Not reported
Duration of study	18 months from January 01, 2012
Age, gender, ethnicity	REBOA: median age (Percentile 25 - 75) 41 (24 - 62); male n(%) 19 (79.2). RT: median age (Percentile 25 - 75) 30.5 (23.5 - 48); male n(%) 63 (87.5)
Patient characteristics	all adult patients (age ≥ 16 years) undergoing resuscitative thoracotomy or REBOA
Intervention	REBOA (n=24) Resuscitative thoracotomy (n=72)
Outcomes	- in hospital mortality - ED mortality

Study	**Matsumara 2017**
Study type	Retrospective cohort study
Number of studies/ number of participants	106 trauma patients
Countries and Settings	DIRECT-IABO Registry has been conducted by the Academic Committee in DIRECT in Japan
Funding	Not reported
Duration of study	From August 2011 to December 2015
Age, gender, ethnicity	REBOA: age median (IQR) 60 (42–75); male n(%) 51 (67) RT + REBOA: age median (IQR) 60 (40–78); male n(%) 20 (67)
Patient characteristics	trauma patients with refractory hemorrhagic shock
Intervention	REBOA (n=76) Resuscitative thoracotomy + REBOA group (n=30)
Outcomes	- in hospital mortality

Study	**Nori 2015**
Study type	Retrospective cohort study
Number of studies/ number of participants	1807 matched patients
Countries and Settings	Japan Trauma Data Bank
Funding	Not reported
Duration of study	Between 2004 and 2011
Age, gender, ethnicity	REBOA: age mean ± sd 51.6 ± 20.6; male n(%) 234 (66.7) No- REBOA: age mean ± 51.8 ± 20.2; male n(%) 974 (66.9)
Patient characteristics	Patients who received a REBOA device with those who did not among a cohort of critically ill adult blunt trauma patients.
Intervention	REBOA (n=351) No-REBOA (n=1456)
Outcomes	- in hospital mortality - Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)

Study	**Yamamoto 2019**
Study type	Retrospective cohort study
Number of studies/ number of participants	234 matched trauma patients [from 82372 patients of trauma register]
Countries and Settings	Japan Trauma Data Bank
Funding	Not reported
Duration of study	Between 2004 and 2016
Age, gender, ethnicity	REBOA: age mean ± sd 52 ± 21; male n(%) 82 (70) No- REBOA: age mean ± 57 ± 23; male n(%) 69 (59)
Patient characteristics	Trauma patients who arrived at each participating center
Intervention	Matched patients: REBOA (n=117); No-REBOA (n=117) [from 385 REBOA and 81986 no-REBOA]
Outcomes	- survival at 28 days - a composite of in-hospital death - trasfusion in number of patients

Elenco degli studi esclusi con motivazione

1	Hidefumi Sano, Junya Tsurukiri, Akira Hoshiai , Taishi Oomura , Yosuke Tanaka , Shoichi Ohta. 2016. Resuscitative Endovascular Balloon Occlusion of the Aorta for Uncontrollable Nonvariceal Upper Gastrointestinal Bleeding	POPULATION
2	Brenner, M., Moore, L., Taylor, J., et al. Exclusive clinical experience with a lower profile device for resuscitative endovascular balloon occlusion of the aorta (REBOA). American journal of surgery 217, 1126-1129.	DUPLICATE
3	Brenner, M., Teeter, W., Hoehn, M., Pasley, J., Hu, P. & Yang, S. Use of resuscitative endovascular balloon occlusion of the aorta for proximal aortic control in patients with severe hemorrhage and arrest. Journal of Vascular Surgery 67, 355-356 (2018).	CONFERENCE PROCEEDINGS/ABSTRACT
4	Campagna Giovanni, A., Cunningham Megan, E., Vogel Adam, M., et al. The utility and promise of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in the pediatric population: An evidence-based review. Journal of pediatric surgery 1, 1531-5037 (2020).	STUDY DESIGN
5	Caulfield, A.R. Does resuscitative endovascular balloon occlusion of the aorta have a place in the prehospital setting for pelvic fracture patients in New Zealand? Trauma (United Kingdom) 18, 301 (2016).	STUDY DESIGN
6	Contrada, E. 1.5 CE Test Hours: The Use of Resuscitative Endovascular Balloon Occlusion of the Aorta in Treating Hemorrhagic Shock from Severe Trauma. The American journal of nursing 118, 29-40.	STUDY DESIGN
7	Daskal, Y., Kessel, B., https://orcid.org, I.O., et al. Potential resuscitative endovascular balloon occlusion of aorta candidates: defining the potential need using the National Trauma Registry. ANZ journal of surgery 90, 477-480.	STUDY DESIGN
8	Davidson Anders, J., Russo Rachel, M., DuBose Joseph, J., et al. Potential benefit of early operative utilization of low profile, partial resuscitative endovascular balloon occlusion of the aorta (P- REBOA) in major traumatic hemorrhage. Trauma surgery & acute care open 1, e000028 (2016).	STUDY DESIGN
9	Dedola, E. & McEwan, J. Resuscitative endovascular balloon occlusion of the aorta : A systematic review of the literature. Journal of the Intensive Care Society 17, 139-140 (2016).	CONFERENCE PROCEEDINGS/ABSTRACT
10	Eccles, A., Jenkins, P.E. & Nutbeam, T. Endovascular balloon aortic occlusion -does it have a role within the emergency departments of a geographically spread trauma network? CardioVascular and Interventional Radiology 42, S242 (2019).	CONFERENCE PROCEEDINGS/ABSTRACT
11	effectiveness, I.T.T. & http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN16184981, c.-e.o.R.E.B.O.o.t.A.f.t.B.	STUDY DESIGN
12	Elias, K. & Engelhardt, M. [Resuscitative endovascular balloon occlusion of the aorta : Bridge to surgery]. "	STUDY DESIGN

	Resuscitative endovascular balloon occlusion of the aorta " : Uberbruckende Massnahme bis zur operativen Versorgung. Der Unfallchirurg 121, 537-543.	
13	Engberg, M., Russell, L., Konge, L., Taudorf, M., Rasmussen, N.K. & Lonn, L. Training in resuscitative endovascular balloon occlusion of the aorta. Acta Anaesthesiologica Scandinavica 63, e20 (2019).	STUDY DESIGN
14	Hsu, C.H., Brenner, M.L., Pasley, J., et al. Use of resuscitative endovascular balloon occlusion of the aorta (REBOA) in refractory shock from pelvic venous hemorrhage. Shock 43, 44 (2015).	CONFERENCE PROCEEDINGS/ABSTRACT
15	Kulla, M., Popp, E. & Knapp, J. Resuscitative endovascular balloon occlusion of the aorta : an option for noncompressible torso hemorrhage ? Current opinion in anaesthesiology 32, 213-226.	STUDY DESIGN
16	Linsenmaier, U., Kanz, K.G., Rieger, J., et al. [CT-guided aortic balloon occlusion in traumatic abdominal and pelvic bleeding]. CT-gesteuerte Ballonokklusion der Aorta bei traumatischen abdominellen und pelvinen Massenblutungen. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 175, 1259-1263.	STUDY DESIGN
17	Long, B., Hafen, L., Koyfman, A. & Gottlieb, M. Resuscitative Endovascular Balloon Occlusion of the Aorta : A Review for Emergency Clinicians. The Journal of emergency medicine 56, 687-697.	STUDY DESIGN
18	Can contrast-enhanced ultrasonography improve Zone III REBOA placement for prehospital care? %B: The journal of trauma acute care surgery	OUT OF SCOPE
19	Manzano-Nunez, R., Orlas Claudia, P., Falla-Martinez Juan, C., et al. Could resuscitative endovascular balloon occlusion of the aorta improve survival among severely injured patients with post-intubation hypotension? European journal of trauma and emergency surgery : official publication of the European Trauma Society 44, 527-533.	STUDY DESIGN
20	Matsushima, K., Inaba, K., Conti, B., Chauhan, R. & Dutton Richard, P. Novel Methods for Hemorrhage Control: Resuscitative Endovascular Balloon Occlusion of the Aorta and Emergency Preservation and Resuscitation. Anesthesiology clinics 37, 171-182.	STUDY DESIGN
21	McGreevy, D.T., Sadeghi, M., Pirouzram, A., et al. Feasibility and Clinical Outcome of Reboa in Patients with Impending Traumatic Cardiac Arrest. Shock 16, 1540-0514 (2019).	OUT OF SCOPE
22	Mill, V. & Montan, C. Potential for Resuscitative Endovascular Balloon Occlusion of the Aorta (Reboa) at a Scandinavian Trauma Referral Center. European Journal of Vascular and Endovascular Surgery 58, e627-e628 (2019).	CONFERENCE PROCEEDINGS/ABSTRACT
23	Nakajima, K., Abe, T., Yamaguchi, K., et al. Does the conventional landmark help to place the tip of REBOA catheter in the optimal position? A non-controlled comparison study. World journal of emergency surgery : WJES 14, 35 (2019).	OUT OF SCOPE

24	Narita, M., Idoguchi, K., Usui, R., Nakao, S. & Mizushima, Y. Safety and efficacy of resuscitative endovascular balloon occlusion of the aorta using a 7-Fr sheath. CardioVascular and Interventional Radiology 39, S188-S189 (2016).	STUDY DESIGN
25	Norii, T., Cameron, C., all & Terasaka, Y. Resuscitative endovascular balloon occlusion of the aorta in pediatric trauma patients. Academic Emergency Medicine 23, S111 (2016).	DUPLICATE
26	Okada, Y., Narumiya, H., Ishi, W., Ryoji, I. & https://orcid.org/---476X, I.O. Lower limb ischemia caused by resuscitative balloon occlusion of aorta. Surgical case reports 2, 130.	STUDY DESIGN
27	O'Neil, M., Vella, M., Dumas, R., Seamon, M., Cannon, J. & Qasim, Z. Long-term outcomes in reboa use: A single-center experience. Critical Care Medicine 47, 2019-2020 (2019).	CONFERENCE PROCEEDINGS/ABSTRACT
28	Orita, T., Funabiki, T., Matsumoto, S., et al. Partial occlusion with reboa strategy for traumatic hemorrhagic shock patients would be feasible and safe, but available for only lower physiological severity patients compared with full occlusion treatment cases. Circulation 136, 2017-2013 (2017).	CONFERENCE PROCEEDINGS/ABSTRACT
29	Orita, T., Funabiki, T., Yamazaki, M., et al. It would be possible to rescue traumatic hemorrhagic shock patients who failed to fluid resuscitation (fluid non-responder) but succeed in REBOA resuscitation (REBOA /IABO responder). Circulation 132, 2015-2011 (2015).	CONFERENCE PROCEEDINGS/ABSTRACT
30	Orita, T., Matsumoto, S., Funabiki, T., et al. Hybrid strategy of damage control IR (DCIR) and. Circulation 138, 2018-2011 (2018).	CONFERENCE PROCEEDINGS/ABSTRACT
31	Qasim, Z., Panichelli, H., Robinson, J., Bradley, K. & Zern Susan, C. Successful Interprofessional Approach to Development of a Resuscitative Endovascular Balloon Occlusion of the Aorta Program at a Community Trauma Center. The Journal of emergency medicine 54, 419-426.	OUT OF SCOPE
32	Renna Maxwell, S., van Zeller, C., Abu-Hijleh, F., Tong, C., Gambini, J. & Ma, M. A one-year cost-utility analysis of REBOA versus RTACC for non-compressible torso haemorrhage. Trauma (London, England) 21, 45-54.	NO OUTCOME OF INTEREST
33	Ribeiro Junior Marcelo Augusto, F., Reis, D.E.-M.R., Rodrigues Vinicius, C., et al. Resuscitative endovascular balloon occlusion of the aorta (REBOA): an updated review. Revista do Colegio Brasileiro de Cirurgioes 45, e1709.	STUDY DESIGN
34	Sambor, M. Resuscitative Endovascular Balloon Occlusion of the Aorta for Hemorrhage Control in Trauma Patients: An Evidence-Based Review. Journal of trauma nursing : the official journal of the Society of Trauma Nurses 25, 33-37.	STUDY DESIGN
35	Samuels, J.M., Sun, K., Moore, E.E., et al. REBOA : Interest Is Wide but Use Remains Limited. Journal of the American College of Surgeons 229, e240-e241 (2019).	OUT OF SCOPE
36	Teeter, W., Romagnoli, A., Glaser, J., et al. Resuscitative Endovascular Balloon Occlusion of the Aorta : Pushing Care Forward. Journal of special operations medicine : a peer reviewed journal for SOF medical professionals	OUT OF SCOPE

	17, 17-21 (2017).	
37	Teeter, W., Romagnoli, A., Wasicek, P., et al. Resuscitative Endovascular Balloon Occlusion of the Aorta Improves Cardiac Compression Fraction Versus Resuscitative Thoracotomy in Patients in Traumatic Arrest. Annals of emergency medicine 72, 354-360.	NO OUTCOME OF INTEREST
38	Teeter William, A., Bradley Matthew, J., Romagnoli, A., et al. Treatment Effect or Effective Treatment? Cardiac Compression Fraction and End-tidal Carbon Dioxide Are Higher in Patients Resuscitative Endovascular Balloon Occlusion of the Aorta Compared with Resuscitative Thoracotomy and Open-Chest Cardiac Massage. The American surgeon 84, 1691-1695.	AWAITING ASSESSMENT
39	Teeter William, A., Matsumoto, J., Idoguchi, K., et al. Smaller introducer sheaths for REBOA may be associated with fewer complications. The journal of trauma and acute care surgery 81, 1039-1045. 2016	NO OUTCOME OF INTEREST
40	Theodorou Christina, M., Anderson Jamie, E., Galante Joseph, M., et al. Practice, Practice, Practice! Effect of Resuscitative Endovascular Balloon Occlusion of the Aorta Volume on Outcomes: Data From the AAST AORTA Registry. The Journal of surgical research 253, 18-25.	NO OUTCOME OF INTEREST
41	True Nicholas, A., Siler, S. & Manning James, E. Endovascular resuscitation techniques for severe hemorrhagic shock and traumatic arrest in the presurgical setting. Journal of special operations medicine : a peer reviewed journal for SOF medical professionals 13, 33-37.	STUDY DESIGN
42	Tsurukiri, J., Akamine, I., Sato, T., et al. Resuscitative endovascular balloon occlusion of the aorta for uncontrolled haemorrahgic shock as an adjunct to haemostatic procedures in the acute care setting. Scandinavian journal of trauma, resuscitation and emergency medicine 24, 13.	DUPLICATE
43	Tsurukiri, J., Sano, H., Akamine, I., Moriya, M., Yamanaka, H. & Hoshiai, A. 7 Fr intra- aortic balloon occlusion catheters for Reboa : A comparison with 10 Fr catheters. Critical Care Medicine 44, 372 (2016).	CONFERENCE PROCEEDINGS/ABSTRACT
44	TW, Costantini; R, Coimbra; JB, Holcomb; JM, Podbielski; R, Catalano; A, Blackburn; TM, Scalea; DM, Stein; L, Williams; J, Conflitti; et al. %T: Current management of hemorrhage from severe pelvic fractures: results of an American Association for the Surgery of Trauma multi-institutional trial %B: The journal of trauma; acute care surgery; Journal: - Volume 0, Issue 0, pp. - published	WRONG INTERVENTION
45	van Oostendorp, S.E., Geeraedts, L.M.G., Jr., https://orcid.org, I.O., Tan, E.C.T.H. & Tan, E.C.T.H. Prehospital control of life-threatening truncal and junctional haemorrhage is the ultimate challenge in optimizing trauma care; a review of treatment options and their applicability in the civilian trauma setting. Scandinavian journal of trauma, resuscitation and emergency medicine 24, 110.	STUDY DESIGN
46	Villamaria Carole, Y., Eliason Jonathan, L., Napolitano Lena, M., Stansfield, R.B., Spencer Jerry, R. & Rasmussen	OUT OF SCOPE

	Todd, E. Endovascular Skills for Trauma and Resuscitative Surgery (ESTARS) course: curriculum development, content validation, and program assessment. The journal of trauma and acute care surgery 76, 929-935; discussion 935-926.	
47	Wasicek Philip, J., Shanmuganathan, K., Teeter William, A., et al. Assessment of Blood Flow Patterns Distal to Aortic Occlusion Using CT in Patients with Resuscitative Endovascular Balloon Occlusion of the Aorta. Journal of the American College of Surgeons 226, 294-308.	STUDY DESIGN
48	Woo, K., Juen Ko, H., Froghi, S., Juen Ko, H. & Froghi, S. Role of resuscitative endovascular balloon occlusion of the aorta in penetrative and blunt trauma resuscitation : A systematic review. British Journal of Surgery 106, 127 (2019).	CONFERENCE PROCEEDINGS/ABSTRACT
49	Barnard Edward Benjamin, G., Morrison Jonathan, J., Madureira Ricardo, M., et al. Resuscitative endovascular balloon occlusion of the aorta (REBOA): a population based gap analysis of trauma patients in England and Wales. Emergency medicine journal : EMJ 32, 926-932.	STUDY DESIGN
50	Beyer Carl, A., Johnson, M.A., Galante Joseph, M. & DuBose Joseph, J. Zones matter: Hemodynamic effects of zone 1 vs zone 3 resuscitative endovascular balloon occlusion of the aorta placement in trauma patients. Injury 50, 855-858.	STUDY DESIGN
51	Brenner, M., Teeter, W., Hoehn, M., et al. Use of Resuscitative Endovascular Balloon Occlusion of the Aorta for Proximal Aortic Control in Patients With Severe Hemorrhage and Arrest. JAMA surgery 153, 130-135.	STUDY DESIGN
52	Cantle Paul, M., Hurley Matthew, J., Swartz Michael, D. & Holcomb John, B. Methods for Early Control of Abdominal Hemorrhage : An Assessment of Potential Benefit. Journal of special operations medicine : a peer reviewed journal for SOF medical professionals 18, 98-104 (2018).	STUDY DESIGN
53	Coccolini, F., Cremonini, C., Chiarugi, M., et al. Aortic balloon occlusion (REBOA) in pelvic ring injuries: preliminary results of the ABO Trauma Registry. Updates in surgery 4, 2038-3312 (2020).	STUDY DESIGN
54	Costantini Todd, W., Coimbra, R., Holcomb John, B., et al. Current management of hemorrhage from severe pelvic fractures: Results of an American Association for the Surgery of Trauma multi-institutional trial. The journal of trauma and acute care surgery 80, 717-723; discussion 723-715.	STUDY DESIGN
55	Darrabie Marcus, D., Croft Chasen, A., Brakenridge Scott, C., et al. Resuscitative Endovascular Balloon Occlusion of the Aorta : Implementation and Preliminary Results at an Academic Level I Trauma Center. Journal of the American College of Surgeons 227, 127-133.	STUDY DESIGN
56	Duchesne, J., Costantini Todd, W., Khan, M., et al. The effect of hemorrhage control adjuncts on outcome in severe pelvic fracture: A multi-institutional study. The journal of trauma and acute care surgery 87, 117-124.	STUDY DESIGN
57	Dumas Ryan, P., Holena Daniel, N., Smith Brian, P., et al. Resuscitative Endovascular Balloon Occlusion of the Aorta : Assessing Need in an Urban Trauma Center. The Journal of surgical research 233, 413-419.	STUDY DESIGN

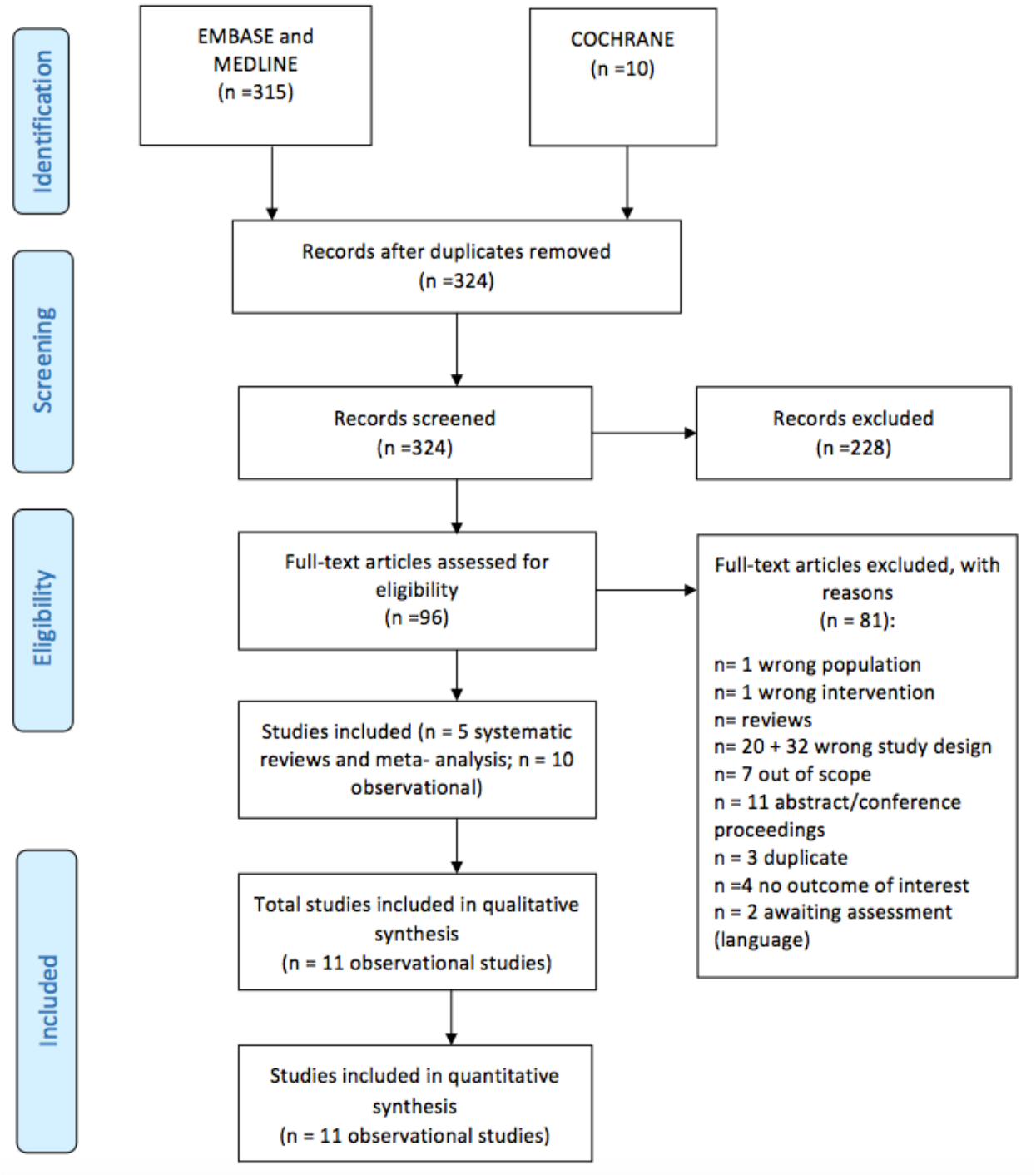
58	Engdahl Ashton, J., Parrino Christopher, R., Wasicek Philip, J., et al. Anesthetic Management of Patients After Traumatic Injury With Resuscitative Endovascular Balloon Occlusion of the Aorta. Anesthesia and analgesia 129, e146-e149.	STUDY DESIGN
59	Fitzgerald, M., Mathew, J., Yeung, M., et al. Feasibility study for implementation of resuscitative balloon occlusion of the aorta in peri-arrest, exsanguinating trauma at an adult level 1 Australian trauma centre. Emergency medicine Australasia : EMA 32, 127-134.	STUDY DESIGN
60	Kono, N., Okamoto, H., Uchino, H., Ikegami, T. & Fukuoka, T. Complications following resuscitative endovascular balloon occlusion of the aorta in patients with polytrauma. Critical Care 21, 235 (2017).	STUDY DESIGN
61	Lendrum, R., Perkins, Z., Davies, G., et al. Pre-hospital Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for exsanguinating pelvic haemorrhage. Resuscitation 135, 6-13.	STUDY DESIGN
62	Matsumoto, S., Moriya, T., https://orcid.org, I.O., et al. Placement accuracy of resuscitative endovascular occlusion balloon into the target zone with external measurement. Trauma surgery & acute care open 5, e000443 (2020).	STUDY DESIGN
63	Matsumura, Y., Matsumoto, J., Kondo, H., et al. Early arterial access for resuscitative endovascular balloon occlusion of the aorta is related to survival outcome in trauma. The journal of trauma and acute care surgery 85, 507-511.	STUDY DESIGN
64	Mill, V., Wellme, E., Montan, C. & https://orcid.org, I.O. Trauma patients eligible for resuscitative endovascular balloon occlusion of the aorta (REBOA), a retrospective cohort study. European journal of trauma and emergency surgery : official publication of the European Trauma Society 23, 1863-9941 (2020).	STUDY DESIGN
65	Moore Laura, J., Martin Clay, D., Harvin John, A., Wade Charles, E. & Holcomb John, B. Resuscitative endovascular balloon occlusion of the aorta for control of noncompressible truncal hemorrhage in the abdomen and pelvis. American journal of surgery 212, 1222-1230.	STUDY DESIGN
66	Morrison, J.J., Morrison, J.J., Midwinter, M.J., et al. Resuscitative endovascular balloon occlusion of the aorta : A gap analysis of severely injured UK Combat casualties. Shock 41, 388-393 (2013).	STUDY DESIGN
67	Norii, T., Miyata, S., Terasaka, Y., et al. Resuscitative endovascular balloon occlusion of the aorta in trauma patients in youth. The journal of trauma and acute care surgery 82, 915-920.	STUDY DESIGN
68	Northern David, M., Manley Justin, D., Lyon, R., et al. Recent advances in austere combat surgery: Use of aortic balloon occlusion as well as blood challenges by special operations medical forces in recent combat operations. The journal of trauma and acute care surgery 85, S98-S103.	STUDY DESIGN
69	Ogura, T., Lefor Alan, K., Nakamura, M., Fujizuka, K., Shiroto, K. & Nakano, M. Ultrasound-Guided Resuscitative Endovascular Balloon Occlusion of the Aorta in the Resuscitation Area. The Journal of emergency medicine 52, 715-722.	STUDY DESIGN

70	Ordonez, C.A.M.D., Nunez, R.M., Parra, M.W., et al. Common complications after the use of resuscitative endovascular balloon occlusion of the aorta (REBOA). Journal of the American College of Surgeons 225, S52 (2017).	STUDY DESIGN
71	Ordonez Carlos, A., Rodriguez, F., Serna Jose, J., et al. Resuscitative Endovascular Balloon of the Aorta is feasible in penetrating chest trauma with major hemorrhage : Proposal of a new institutional deployment algorithm. The journal of trauma and acute care surgery 27, 2163-0763 (2020).	STUDY DESIGN
72	Park, Y., Yu, B., Lee, G., et al. Implementation of resuscitative endovascular balloon occlusion of the aorta at the Korean Regional Trauma Center. Hong Kong Journal of Emergency Medicine 20, 1024-9079 (2019).	STUDY DESIGN
73	Pieper, A., Thony, F., Brun, J., et al. Resuscitative endovascular balloon occlusion of the aorta for pelvic blunt trauma and life-threatening hemorrhage : A 20-year experience in a Level I trauma center. The journal of trauma and acute care surgery 84, 449-453.	STUDY DESIGN
74	Sadeghi, M., Maszkowski, M., Bersztel, A., et al. The use of aortic balloon occlusion in traumatic shock : first report from the ABO trauma registry. European journal of trauma and emergency surgery : official publication of the European Trauma Society 44, 491-501.	STUDY DESIGN
75	Saito, N., Matsumoto, H., Yagi, T., et al. Evaluation of the safety and feasibility of resuscitative endovascular balloon occlusion of the aorta. The journal of trauma and acute care surgery 78, 897-903; discussion 904.	STUDY DESIGN
76	Sato, R., Iwanaga, W., https://orcid.org, I.O., et al. Resuscitative endovascular balloon occlusion of the aorta performed by emergency physicians for traumatic hemorrhagic shock : a case series from Japanese emergency rooms. Critical care (London, England) 22, 103.	STUDY DESIGN
77	Shoji, T., Tarui, T., Igarashi, T., et al. Resuscitative Endovascular Balloon Occlusion of the Aorta Using a Low-Profile Device is Easy and Safe for Emergency Physicians in Cases of Life-Threatening Hemorrhage. The Journal of emergency medicine 54, 410-418.	STUDY DESIGN
78	Siddiqui, J., Cross, S., Low, D.E. & Fotheringham, T. The resuscitative balloon occlusion of the aorta (REBOA): Experience in a UK major- trauma centre. CardioVascular and Interventional Radiology 38, S205-S206 (2015).	STUDY DESIGN
79	Thabouillot, O., Bertho, K., Rozenberg, E., et al. How many patients could benefit from REBOA in prehospital care? A retrospective study of patients rescued by the doctors of the Paris fire brigade. Journal of the Royal Army Medical Corps 164, 267-270. 2018	STUDY DESIGN
80	Wasicek Philip, J., Li, Y., Yang, S., et al. Examination of hemodynamics in patients in hemorrhagic shock undergoing Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). Injury 50, 1042-1048.	STUDY DESIGN
81	Kulla, M., Holstrater, T., Engelhardt, M., et al. Do we need REBOA as an adjunct to ER thoracotomy in German trauma centres? A secondary data analysis from the TraumaRegister DGU®. Anasthesiologie und Intensivmedizin 59, 562-573 (2018).	AWAITING ASSESSMENT

Appendice C - Sintesi delle evidenze

CQ7: Controllo dell'emorragia nel setting pre- e intraospedaliero: REBOA

Figure 1. Flow Chart of study selection



È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono stati individuati 324 records. Fra questi, sono state individuate 5 revisioni sistematiche di studi osservazionali (van der Burg 2018, Gamberini 2017, Morrison 2016, Manzano Nunez 2017, Manzano Nunez 2018). Nessuno studio randomizzato controllato. Un protocollo di trial registrato ma sospeso (ISRCTN16184981). In totale sono stati esclusi 52 per disegno di studio errato di cui 32 serie di casi/1 coorte. Due studi rimangono in awaiting assessment dal momento che non sono stati reperiti i full text (Kulla 2019 e Teether 2018) (**Appendice B**, Lista degli Esclusi).

Alla fine, uno studio osservazionale proveniente da precedenti revisioni sistematiche è stato preso in considerazione ed aggiunto agli studi inclusi per un totale complessivo di 11 studi osservazionali comparativi (**Appendice B**, Lista degli Inclusi).

Riassumendo, in tutto:

- 5 studi inclusi valutano la comparazione Resuscitative endovascular balloon occlusion of the aorta (REBOA) vs resuscitative thoracotomy (RT);
- Uno studio incluso valuta la comparazione REBOA vs RT + REBOA;
- 5 studi inclusi valutano la comparazione REBOA vs no-REBOA.

Nella tabella seguente sono rappresentate le descrittive dei PICO di interesse nelle caratteristiche generali degli studi inclusi **(tabella 1**).

Studio	Disegno di studo	Setting	Popolazione	Intervento	Confronto	Outcome e Tempo misurazione
Brenner 2018	✓ prospective observational	Resuscitation in Trauma and Acute Care Surgery (AORTA) study was approved by the American Association for the Surgery	Adult trauma and acute care surgery (age ≥ 18) patients undergoing aortic occlusion (AO) in the acute phases after injury were enrolled Blunt trauma was common (58.6% of which 83% REBOA group and 48.5% RT) ISS= mean 38.2 (SD:18.9)	REBOA (n = 83) Unclear modality of intervention (full/partial)*	RT (n = 202)	✓ in-hospital mortality ✓ Complication ✓ Units packed red blood cells ✓ Units fresh frozen plasma ✓ Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)
Aso 2017	✓ retrospective cohort study ✓ propensity score-adjusted Cox regression analysis (logistic regression model for the receipt of REBOA or RT as a function of the following conditions and interventions performed on day 0 or 1: age, sex, BMI, etiology, JCS, presence of head injury, presence of cardiopulmonary arrest	data from a national inpatient database in Japan	Trauma patients with uncontrolled hemorrhagic shock (n = 259) excluded penetrating thoracic injuries Blunt trauma (100%) ISS=missing information	REBOA (n = 191) Unclear modality of intervention (full/partial)	RT (n = 68)	✓ in-hospital mortality ✓ ventilator-free days (VFDs) ✓ intensive care unit (ICU)-free days ✓ total amount of fluid infusion within 1 day after admission (mL) ✓ total amount of transfusion within 1 day after admission (mL) ✓ total hospitalization

	on admission, TMPM-ICD9, and annual number of patients receiving RT at each hospital.					costs
Abe 2016	✓ retrospective cohort study ✓ propensity score matching (three adjustment models: RTS-adjusted model, an ISS-adjusted model, and TRISS-adjusted model)	Japan Trauma Data Bank (JTDB) nationwide trauma registry	Trauma patients (n= 903) Blunt trauma was common (838/895; 93.6%). ISS= mean 34 (SD:25);mean 34 (SD:20)	REBOA (n = 636) Unclear modality of intervention (full/partial)	resuscitative open aortic cross-clamping (RT) (n = 267)	✓ in-hospital mortality ✓ ED mortality ✓ Blood transfusion
DuBose 2016	✓ prospective observational	multcenter data from Trauma and Acute Care Surgery registry (8 American College of Surgeons level I centers).	Adult trauma and acute care surgery (age ≥ 18) patients undergoing aortic occlusion (AO) in the acute phases after injury (n=114) Blunt trauma (62.3%) ISS= median 31.0(IQR:30);median 31.5 (IQR:22)	REBOA (n = 46) Unclear modality of intervention (full/partial)	AO (n=68)	✓ Hemodynamic stability ✓ Improvement in hemodynamicsred blood cell requirements ✓ in hospital mortality ✓ ED mortality ✓ Complications ✓ Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)
Moore 2015	✓ retrospective cohort study	Trauma registry from two Level 1 trauma centers (Texas and MarylandYBaltimore).	Trauma patients in NCTH (n=96) Blunt trauma (44.4% RT; 66.7% REBOA) ISS= median 34 (IQR:27-59); median 28 (IQR:17-43)	REBOA (n=24) Unclear modality of intervention (full/partial)	RT (n=72)	✓ in hospital mortality ✓ ED mortality
Matsumara 2017*	✓ retrospective cohort study	DIRECT-IABO Registry has been conducted by the Academic Committee in DIRECT in Japan	Trauma patients with refractory hemorrhagic shock Blunt trauma (96%) ISS= median 36 (IQR: 28–50); 44 (IQR: 38–59)	REBOA (n=76) Partial occlusion (70% of participants)*	RT +REBOA group (n=30)	✓ in hospital mortality
Nori 2015	✓ retrospective cohort study	Japan Trauma Data Bank	critically uncontrolled hemorrhagic shock	REBOA (n=351)	control group	✓ in hospital mortality

	✓ propensity score matching analysis (age, sex, calendar year,Revised Trauma Score (RTS),mechanism of injury (e.g., traffic crash, fall),maximumAIS for each of the nine body regions, and treating facility to calculate the PS).		limited to blunt trauma patients. Blunt trauma (100%) ISS= mean 32.4 (SD:16.4)	Unclear modality of intervention (full/partial)	(n=1456)	✓ Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)
García 2020	✓ retrospective cohort study ✓ A propensity score was calculated after adjusting for age, clinical signs on admission (systolic blood pressure, cardiac rate, Glasgow coma scale), severe trauma in thorax and abdomen, and the presence of non-compressive torso hemorrhage. Subsequently, logistic regression for mortality was adjusted for the number of red blood cells (RBC) transfused within the first six hours after admission, injury severity score (ISS), and quintiles of PS.	clinical records at Fundación Valle del Lili University hospital in Cali, Colombia level-I trauma center from Colombia.	patients with torso trauma who underwent surgical intervention for hemorrhage control excluded blunt trauma. Penetrating trauma (100%) ISS= median 25 (IQR: 16–25)	REBOA (n=28) Partial occlusion*	control group (n=317)	✓ in hospital mortality ✓ PRBCsA in first 6 h ✓ PlasmaA in first 6 h ✓ PlateletsA in first 6 h ✓ CryoA in first 6 h ✓ Crystalloids in first 24 h ✓ Thoracic damage control ✓ Abdominal damage control ✓ complications
Inoue 2016	✓ retrospective cohort study ✓ A propensity score	Japan Trauma Data Bank	patients with severe torso trauma Blunt trauma (93.8%) ISS= median 35 (IQR: 25–50); median 36 (IQR: 25–50)	REBOA (n=625) Unclear modality of intervention*	control group (n=625)	✓ in hospital mortality ✓ ED mortality
Joseph 2019	✓ case-control retrospective analysis ✓ propensity score: 1:2 ratio using propensity score matching for demographics, vital signs, mechanism of injury, injury severity score, head abbreviated injury scale score, each body region abbreviated injury scale score, pelvic fractures, lower extremity vascular injuries and fractures,	ACSTQIP database and identified all patients who received REBOA within 1 hour of admission	trauma patients after REBOA placement Blunt trauma (95%) ISS= median 28 (IQR:17-35) ; median 29 (IQR:18-38)	REBOA (n=140) Unclear modality of intervention*	control group (n=280)	✓ in hospital mortality ✓ ED mortality ✓ transfusion requirements at 4 hours and 24 hours after injury, ✓ in-hospital complications (deep venous thrombosis, pulmonary embolism, stroke,myocardial infarction, extremity

	and number and grades of intra-abdominal solid organ injuries					compartment syndrome ✓ Health related quality of life (neurologic outcomes: Glasgow Coma Outcomes Score)
Yamamoto 2019	✓ retrospective cohort study ✓ propensity score matching analysis using multivariate logistic regression	Japan Trauma Data Bank	severely injured patients Blunt trauma (96% REBOA; 94% controls) ISS= mean 35 (SD: 13); 33 (SD: 11)	REBOA (n=117)	control group (n=117)	✓ survival at 28 days ✓ a composite of in-hospital death ✓ trasfusion in number of patients

ACRONIMI:

AO=Open Aortic occlusion

ACC= resuscitative open aortic cross-clamping

BMI= body Mass Index

JCS=Japan Coma Scale

NCTH=Noncompressible torso hemorrhage

RTS=revised trauma score

RT= resuscitative thoracotomy with aortic cross-clamping

TMPM-ICD9= the Trauma Mortality Prediction Model based on the ICD 9th Revision

TRISS= trauma and injury severity score

NOTE:

Modality of intervention: REBOA - Unclear modalities of occlusion.*

Brenner 2018. It appears that a longer duration of AO, up to approximately 60 minutes at Zone 1, is tolerated without detriment to survival. It is unknown if, and what percentage of time, did partial occlusion play a role in these REBOA patients. While it is likely that a combination of full and partial AO will prolong the ability to provide proximal control without irreversible distal ischemia, further investigation is needed to determine the consequences of full versus partial occlusion.

Garcia 2020. Partial occlusion is employed to maintain a systolic blood pressure between 80 to 100 mmHg, particularly in subjects with a hemorrhage proximal to the level of occlusion. To this end, the balloon is deflated slightly, allowing a degree blood flow below the occlusion level by progressively removing saline from the balloon. The progressive deflation of the balloon allows a gradual drop in blood pressure to the target value desired (SBP between 80 to 100 mmHg).

Matsumara 2017. The balloon was initially inflated at zone I in 93%, and partial occlusion was performed in 70% of our population. In the setting of zone I with partial occlusion, shorter occlusion (<30 min) might be safer and prolonged occlusion might be associated with worse outcomes.

Inoue 2016. Discussions section – limitations: "he JTDB did not provide detailed data concerning REBOA such as time of insertion, duration of balloon occlusion, and level of balloon occlusion (zone7), method of occlusion (e.g., full/partial, intermittent/continuous), complications regarding insertion and occlusion, and cause of death."

Joseph 2019. There is still a lack of clinical data that adequately address the appropriate use of REBOA and guide the absolute duration of full or partial aortic occlusion.

Critical outcomes

1. Mortality

Tutti gli studi (n=11) hanno riportato dati inerenti la mortalità (tabella 1). La maggior parte di questi (n=9) non ha riportato il tempo di valutazione definendola alla dimissione senza un lasso di tempo specifico (at discharge/overall), mentre 4 studi definiscono il tempo di valutazione a 24 ore (tabella 2), 5 studi valutano la mortalità in emergency department (tabella 3) e 3 studi riportano i dati a 1 mese (tabella 4).

- **Overall mortality**

In figura 1 sono riportate le analisi quantitative della mortalità in-hospital degli studi che hanno fornito dati aggiustati per matching con il propensity score oppure tramite regression (tabella 1). In figura 2 analisi di sensibilità per spiegare il comportamento dell'eterogeneità trovata in figura 1, escludendo studi che disperdevano l'effetto.

Tabella 2. Overall in-hospital mortality. *Data are collected for the last available observation when time of follow up is specified.*

Overall mortality	**REBOA**		**Control**		**time**	**OR Adjusted/Matched**	**Description of adjustement**
	N	**tot**	**n**	**tot**			
Aso 2017	90	191	48	68	Not reported	Hazard ratio= 0.94; 95%CI = 0.60–1.48 § OR 0.821; 95% CI 0.306–1.234	Adjusted Propensity score
Brenner 2018	75	83	197	202	24 h	OR=0.24; 95% CI 0.08 – 0.75	None
Abe 2016	405	636	210	267	Not reported ED	OR 0.261 95%CI 0.130-0.523 Pairs matched n=304	Adjusted Propensity score
DuBose 2016	33	46	57	68	ED 24 h	OR= 0.263; 95% CI= 0.043 – 1.609	not reported (regression)
Moore 2015	15	24	65	72	Not reported ED	none	none
Matsumara 2017	41	76	27	30	-24 h -1 month -discharge	none	none
Nori 2015*	259	351	709	1456	Not reported	OR=2.97; 95% CI= 2.29 – 3.84 Pairs matched 1:5	Adjusted Propensity score
García 2020	5	28	48	317	Not reported	OR=0.20; 95%CI 0.05–0.77	Adjusted Propensity score
Inoue 2016*	386	625	283	625	Not reported ED	OR=1.95, 95% CI 1.56-2.45	Adjusted Propensity score
Joseph 2019*	50	140	53	280	ED Overall	OR= 2.38; 95% CI= 1.51 – 3.76	Adjusted Propensity score

Yamamoto 2019*	64	117	79	117	Not reported	OR= 0.58; 95% CI= 0.34 – 0.99	Adjusted Propensity score

§ To be able to pool the adjusted odds ratios in a meta-analysis, the hazard ratio reported in the study by Aso was converted to an odds ratio. For the procedure, we assumed that the hazard ratio is a type of relative risk and, thus, is asymptotically similar to a relative risk. Then, using the inverse probability weighted binomial model we transformed the adjusted hazard ratio of mortality reported in the study by Aso to an odd ratio. Following this approach, we obtained an adjusted odds ratio of mortality (Aso: OR 0.821; 95% CI 0.306–1.234).

* data were reported only for marched pairs

° data variables are described as medians and bootstrapped 95% confident intervals

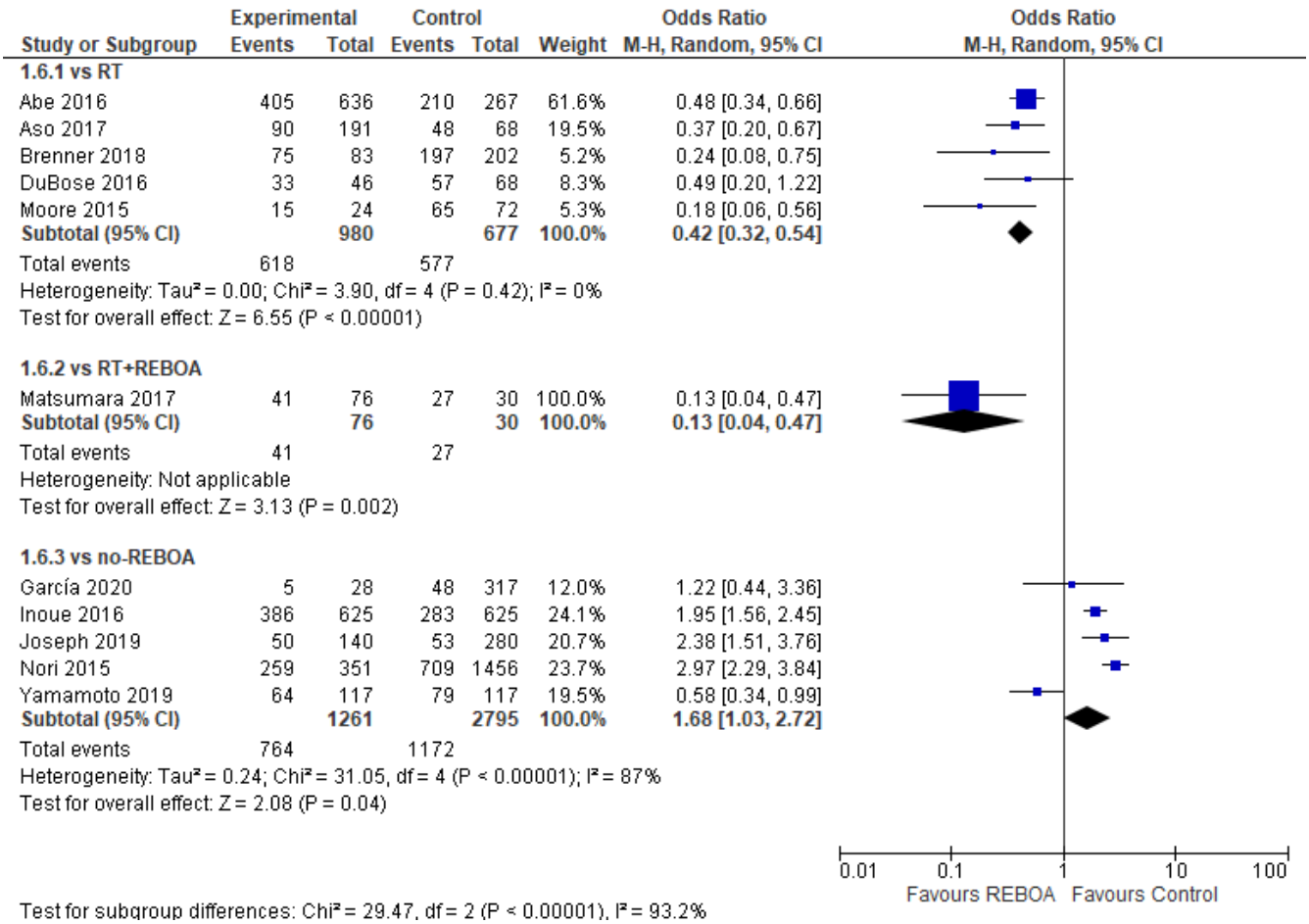


Figure 1. Overall crude odds ratios for in-hospital mortality (REBOA vs control - subgroups)

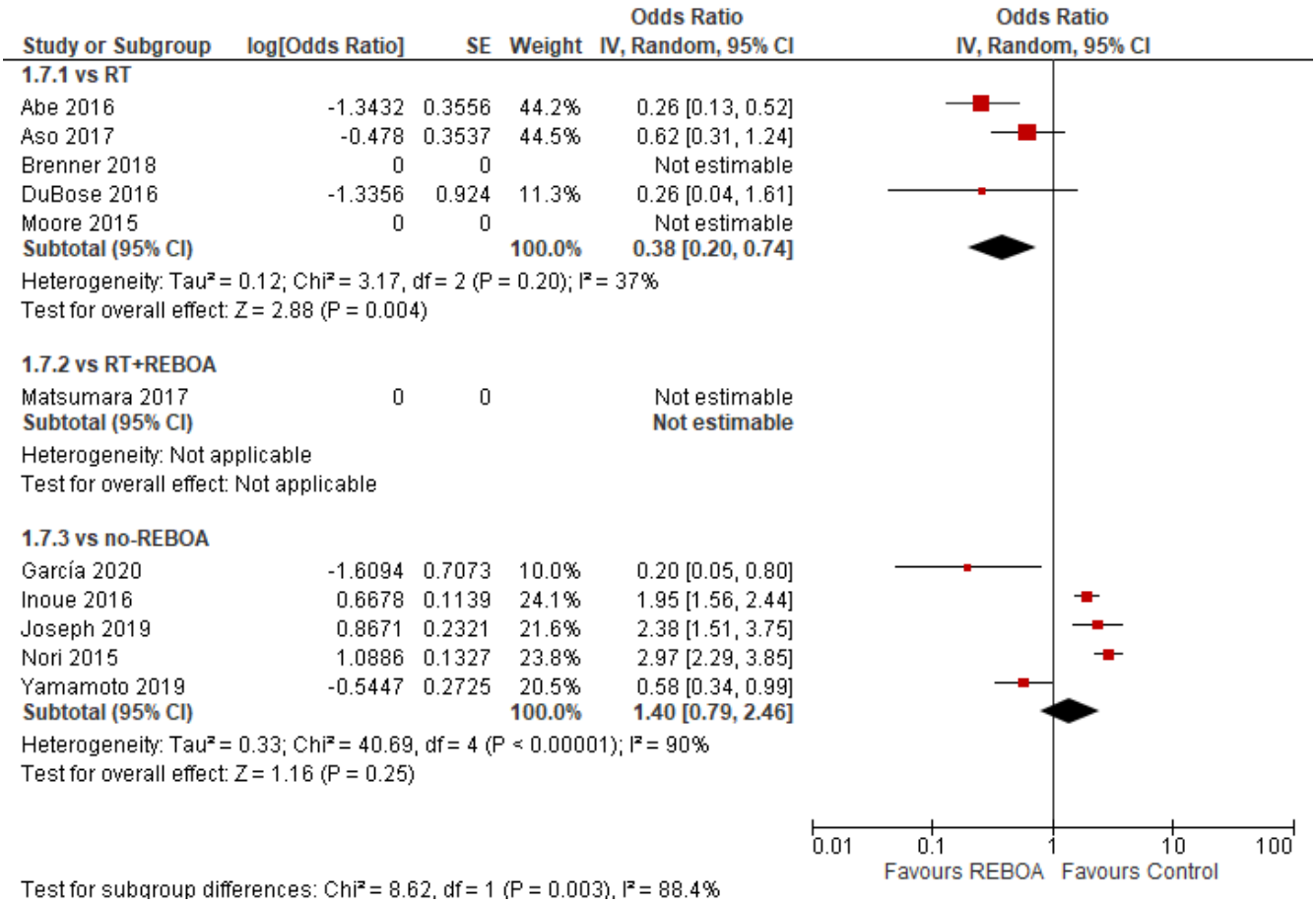


Figure 2. Overall adjusted odds ratios for in-hospital mortality (REBOA vs control- subgroups)

- **Mortality in Emergency Department**

Tabella 3. Mortality in Emergency Department

	REBOA		Control *		Adjusted estimate	Description of adjustment
	n	tot	n	tot		
Abe 2016	137	636	130	267	OR 0.182 95%CI 0.106-0.31 n=299/304	Propensity score
DuBose 2016	25	46	31	68	none	none
Moore 2015	4	24	45	72	none	none
Inoue 2016*	107	625	61	625	OR 1.91, 95% CI 1.36 – 2.67	Propensity score
Joseph 2019	4	140	5	280	OR 1.62 95% CI 0.43 – 6.12	Adjusted Propensity score

§ data variables are described as medians and bootstrapped 95% confident intervals

* **RT (**Abe 2016, DuBose 2016, Moore 2015), **non-REBOA** (Inoue 2016, Joseph 2019).

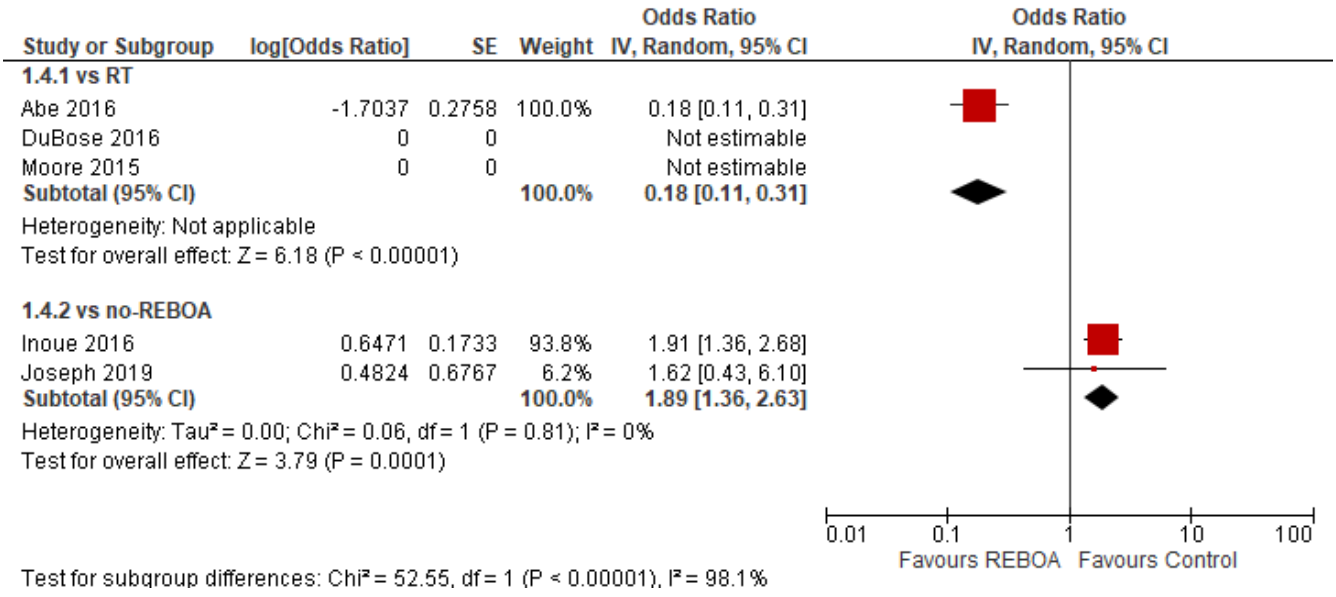


Figure 3. Adjusted odds ratios of mortality for mortality in ED

- **Mortality at 24h**

Tabella 4 Mortality at 24 h

	REBOA		Control*		Adjustment	Description of adjustement
	n	tot	n	tot		
Joseph 2019	37	140	33	280	OR 2.69, 95% CI 1.59 – 4.53	Adjusted Propensity score
Matsumara 2017	30	76	24	30	none	none
Dubose 2016	33	46	57	68	OR= 0.263; 95% CI= 0.043 – 1.609	Adjusted (regression)
Brenner 2018	75	83	197	202	none	none

***RT (**DuBose 2016, Brenner 2018), **RT+REBOA (**Matsumara 2017), **non-REBOA (**Joseph 2019).

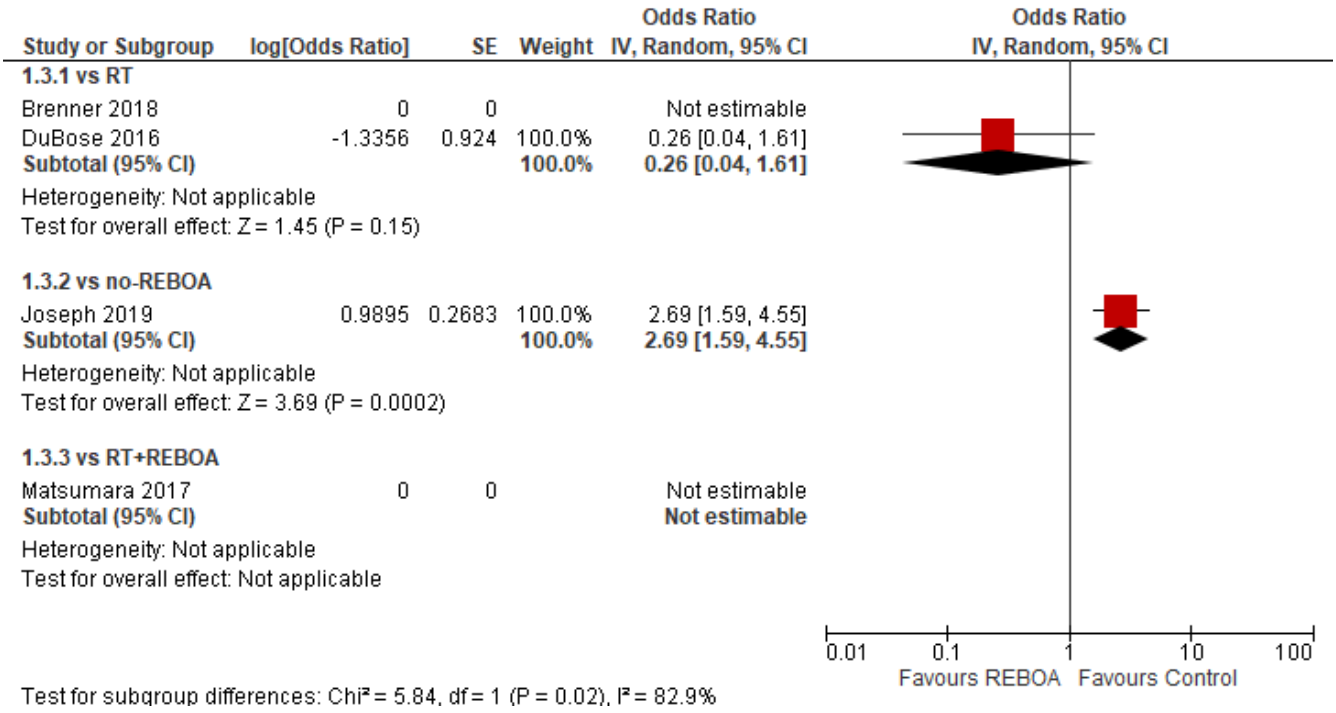


Figure 4. Adjusted odds ratios for mortality at 24h

- **Mortality at 1 month**

Tabella 5. Mortality at 1 month

Overall mortality at discharge	**REBOA**		**Control***		**Adjustment**	**Description of adjustement**
	n	**tot**	**n**	**tot**		
Yamamoto 2019	62	117	78	117	OR 0.56, 95% CI 0.33 – 0.96	Adjusted Propensity score
Matsumara 2017	37	76	27	30	none	
Joseph 2019 §	9	140	15	280	OR 1.21, 95%CI 0.52 – 2.85	Adjusted Propensity score

§ after 24 h

*** RT+REBOA (**Matsumara 2017), **non-REBOA (**Yamamoto 2019, Joseph 2019)

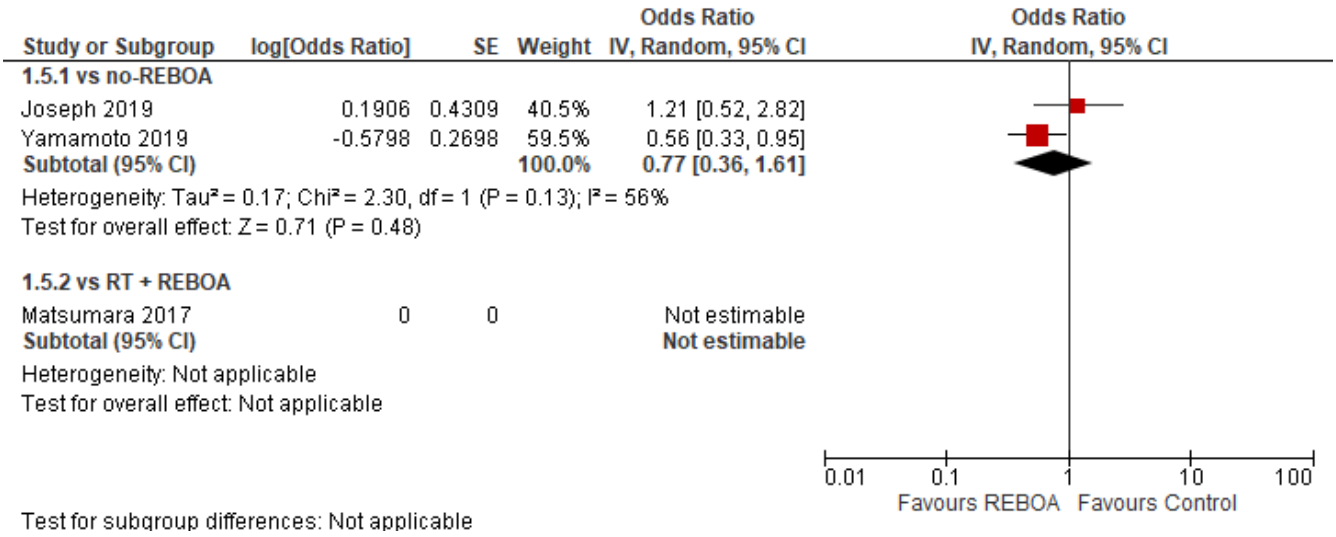


Figure 5. Adjusted odds ratios for mortality at 1 month

2. Volume of blood components

In totale 6 studi indagano l'outcome di interesse.

Tabella 6. Volume of blood components.

Autore	Outcome	Units	REBOA	Control *	p value
cryoprecipitate					
Dubose 2016	cryoprecipitate 24 h	median (IQR)	1(11)	0(1)	0,14
Garcia 2020	cryoprecipitate 6h	median (IQR)	6.5(0-10)	0(0-0)	0,21
crystalloids					
Garcia 2020	crystalloids 24 h mliters	median (IQR)	4649(3290-6329)	4420(2705-6350)	0,13
Dubose 2016	crystalloids- liters 24 h liters	median (IQR)	4(5)	3(5)	0,12
plasma					
Joseph 2019	plasma 24h	median (IQR)	9(6-20)	10(7-20)	0,17
Brenner 2018	plasma 24h	median (IQR)	9 (16)	4 (9)	0,11
DuBose 2016	plasma 24h	median (IQR)	14.5(18)	6(18)	<0.001
Joseph 2019	plasma 4h	median (IQR)	3 (2-5)	3(2-6)	0,001
Garcia 2020	plasma 6h	median (IQR)	4(2.5-6)	0(0-4)	<0.001
platelets					
Joseph 2019	platelets 24h	median (IQR)	7(3-13)	8(3-12)	<0.001
DuBose 2016	platelets 24h	median (IQR)	5.5(12)	1.5(11)	0,5
Joseph 2019	platelets 4h	median (IQR)	4(3-9)	4(3-8)	0,05
Garcia 2020	platelets 6h	median (IQR)	0.5(0-6)	0(0-0)	0,05
PRBCs					
Joseph 2019	PRBCs 24 h	median (IQR)	9(5-20)	10(4-21)	0,3988
Brenner 2018	PRBCs 24 h	median (IQR)	10 (21)	7.8 (10)	0,654
DuBose 2016	PRBCs 24 h	median (IQR)	20.5(18)	13.5(18)	0,343
Joseph 2019	PRBCs 4 h	median (IQR)	6 (3-8)	7(3-9)	0,872
Garcia 2020	PRBCs 6 h	median (IQR)	5(3-9)	2(0-4)	0,149
Total amount of transfusion					
Aso 2016	Total amount of transfusion within 1 d after admission: average (SD), mL	media (sd)	2.396 (1.872)	2.820 (2.782)	0,697
Trasfusion in number of patients					
Abe 2016	trasfusion in number of patients	n (%)	542 (85%)	197(74%)	0,001
Yamamoto 2019	trasfusion in number of patients	n (%)	111(95%)	113 (97%)	<0,001

***RT (**Abe 2016, Aso 2016, DuBose 2016, Brenner 2018), **RT+REBOA (**Matsumara 2017), **non-REBOA (**Yamamoto 2019, Joseph 2019, Garcia 2020).

3. **Health related quality of life** (Discharge GCS)

L'outcome Discharge Glasgow Coma Scale fra i sopravvissuti, come proxy della qualità di vita, è stato riportato da quattro studi (DuBose 2016, Brenner 2018, Nori 2015, Joseph 2019).
In Dubose 2016 nessuna differenza significativa è stata trovata fra i due gruppi in (median REBOA 15 and median Control 15, p=0.766). Brenner 2018 riporta dati inerenti Discharge Glasgow Coma Scale fra i sopravvissuti solo per la coorte pre-hospital trovando una differenza statisticamente significativa (median REBOA 9 and median Control 3, p=0.026).
Nori 2015 e Joseph 2019 riportano i dati delle sottoanalisi dei soli pazienti che hanno ricevuto il REBOA. In Nori 2015 i pazienti che sopravvivono hanno una scala Glasgow Coma Scale (GCS) significativamente più alta rispetto a chi non sopravvive (mean GCS, 11.6 vs. 7.2; p =0.0001) così come Joseph 2019 (p=0.04).

4. Adverse effects

Brenner 2018, Dubose 2016, Joseph 2019 riportano aventi avversi per entrambi I gruppi a confronto. García 2020 riporta gli eventi avversi solo per il gruppo REBOA. Le complicazioni più frequentemente riportate da questi studi sono amputazione, ematoma e pseudoaneurisma riportate in tabella 7.

Tabella 7. The most reported adverse events

	REBOA	*Control*	*p-value*
Need of amputation			
Brenner 2018	*1 (1.2%)*	-	
DuBose 2016	*0 (0%)*	-	
Joseph 2019	*5 (3.6%)*	*2 (0.7%)*	*0.04*
Hematoma			
Brenner 2018	*0 (0%)*	-	
DuBose 2016	*0 (0%)*	-	
Pseudoaneurism			
Brenner 2018	*0 (0%)*		
DuBose 2016	*1 (2.2%)*		

Tabella 8. Adverse events in Brenner 2018

Complication	**N = 83**	
REBOA/endovascular specific complication	**n**	**%**
Hematoma	0	0
Pseudoaneurysm	0	0
Arteriovenous fistula	0	0
Extremity ischemia	1	1.2
Stenosis	0	0
Distal embolism	4	4.8
Infection requiring antibiotics only	1	1.2
Need for patch angioplasty	2	2.4
Need for arterial bypass	0	0
Need for amputation	1	1.2
RT complications		
Retained hemothorax requiring operative evacuation via VATS or thoracotomy	3	1.5
Empyema	0	0
Local wound infection requiring surgery	0	0
Endovascular elements of access		
Access site, femoral	83	100
Access side		
Left	17	20.5
Right	62	74.7
Cut-down utilized	39	47.0
Ultrasound guided percutaneous	12	14.5
Percutaneous using external landmark and palpation	23	27.7
Fluoroscopic guided	0	0
Type of balloon catheter utilized		
Coda™	49	59.0
Reliant™	5	6.0
Prytime ER-REBOA™	22	26.5
Other/not otherwise specified	7	8.4
Imaging utilized to facilitate positioning of balloon for AO		
Plain film	47	56.6
C-arm flouroscopy	1	1.2
None, blind insertion using external landmark only	26	31.3
Ultrasound	3	3.6
Successful AO achieved	78	94.0
Balloon migration observed	3	3.6

Tabella 9. Adverse events in DuBose 2016

Endovascular specific complications (n = 46)	
Hematoma, n (%)	0/46 (0%)
Pseudoaneurysm, n (%)	1/46 (2.2%)
Arteriovenous fistula, n (%)	0/46 (0%)
Extremity ischemia, n (%)	0/46 (0%)
Stenosis, n (%)	0/46 (0%)
Distal embolism, n (%)	2/46 (4.3%)
Infection requiring antibiotics only, n (%)	0/46 (0%)
Need for patch angioplasty, n (%)	0/46 (0%)
Need for arterial bypass, n (%)	0/46 (0%)
Need for amputation, n (%)	0/46 (0%)
Open access complications (n = 68)	
Retained hemothorax requiring operative evacuation via VATS or thoracotomy, n (%)	1/68 (1.4%)
Empyema, n (%)	0/68 (0%)
Local wound infection requiring surgery, n (%)	2/68 (2.9%)

Tabella 10. Adverse events in García 2020

Variable	REBOA ($n=28$)
Arterial access	
Open	25 (89.3%)
Percutaneous	3 (10.7%)
Insertion time, min, median (IQR)	10 (5–25)
Place of inflation, *n* (%)	
Zone I	16 (60.7%)
Zone I and III	11 (39.3%)
Systolic blood pressure, mm Hg, median (IQR)	
Pre insertion	51 (40–65)
Post insertion	110 (91–164)
Duration of inflation, min, median (IQR)	41 (25–55)
Surgical approach, *n* (%)	
Sternotomy	9 (32.1%)
Sternotomy and cervicotomy	3 (10.7%)
Thoracotomy	2 (7.1%)
Laparotomy	18 (64.2%)
Complications related to groin access[A], *n* (%)	2 (7.1%)
Renal Replacement Therapy, *n* (%)	1 (3,5)
Mortality, *n*(%)	5 (17.9%)

A Iatrogenic artery injury with hematoma formation

Tabella 11. Adverse events in Joseph 2019

Variable	Patients, No. (%) No-REBOA Group (n = 280)	REBOA Group (n = 140)	*P* Value
Complications			
Acute kidney injury	9 (3.2)	15 (10.7)	.02
Amputation of lower limb	2 (0.7)	5 (3.6)	.04
Deep venous thrombosis	14 (5.0)	6 (4.3)	.42
Pulmonary embolism	5 (1.8)	2 (1.4)	.28
Stroke	3 (1.1)	2 (1.4)	.37
Myocardial infarction	1 (0.4)	0	.51
Extremity compartment syndrome	2 (0.7)	1 (0.7)	.39

5. Time to temporary control of hemorrhage

Tabella 12. Time to control haemorrhage in Joseph 2019

Variable	Patients, No. (%) No-REBOA Group (n = 280)	REBOA Group (n = 140)	*P* Value
4-h Transfusion, median (IQR), U			
PRBCs	7 (3-9)	6 (3-8)	.14
Platelets	4 (3-8)	4 (3-9)	.13
Plasma	3 (2-6)	3 (2-5)	.17
24-h Transfusion, median (IQR), U			
PRBCs	10 (4-21)	9 (5-20)	.21
Platelets	8 (3-12)	7 (3-13)	.12
Plasma	10 (7-20)	9 (6-20)	.11
Hemorrhage control intervention			
Angioembolization	85 (30.4)	40 (28.6)	.18
Time to angioembolization, median (IQR), min	46 (31-69)	59 (39-78)	.04
Laparotomy	190 (67.9)	96 (68.6)	.33
Time to laparotomy, median (IQR), min	33 (26-62)	45 (35-69)	.04

Tabella 13. Time to control haemorrhage in Matsumara 2017

Characteristics and outcomes	REBOA alone (*N* = 76)	RT + REBOA (*N* = 30)	*P*
Time course (min)			
Arrival to REBOA	60 (27–85)	32 (20–63)	0.026
Arrival to definitive care	71 (50–101)	25 (11–60)	< 0.001

Inoltre, Matsumara et al 2017 riporta il tempo di controllo dell'emorragia dall'arrivo alla scena. Gli stessi autori riportano in discussione: "The shorter arrival to access time and lower ISS were significantly associated with increased survival in hemorrhagic patients undergoing REBOA. Patients with arterial access obtained within 21.5 minutes from arrival demonstrated prompt subsequent hemostasis and better survival curves. Proactive early access in the resuscitation phase may be associated with survival outcomes."

Important outcomes:

1. **Mortality at 12 months:** none reported

2. **Improvement in haemodynamic (bloodpressure and heart rate)**

Tabella 14. Improvement in haemodynamic

	REBOA (n=46)	**RT (n=68)**	**P value**
Dubose 2016			
Improvement in hemodynamics with aortic occlusion, n (%)	29(67.4%)	42(61.8%)	0.544
Hemodynamic stability (SBP consistently above 90 mm Hg) achieved with aortic occlusion, n (%)	22 (51.2%)	19(27.9%)	0.014
Hemodynamic improved with 2ndaortic occlusion, n (%)	2/2 (100%)	7/9 (77.8%)	0.244
Hemodynamic stability (SBP consistently > 90 mm Hg) achieved with 2nd aortic occlusion, n (%)	2/2 (100%)	6/9 (66.7%)	0.217
	REBOA (n=83)	**RT (n=202)**	
Brenner 2018			
Post-occlusion SBP (mean/sd) mmHg	89 (65)	30 (51)	P<0.001
Duration of aortic occlusion, min, median IQR	31 (57)	19 (21)	0.002

3. **Failure/success of REBOA technique**

Questo outcome è presente in due studi che riportano il numero di soggetti in cui la tecnica è stata eseguita con successo.

Tabella 15. Failure/success of REBOA technique.

Successful aortic occlusion	**REBOA n (%)**
Brenner 2018	78/83 (94)
Dubose 2016	42/46 (91.3)

Appendice D - Valutazione della qualità metodologica degli studi inclusi

CQ7: Controllo dell'emorragia nel setting pre- e intraospedaliero: REBOA

Tabella 1. Studi osservazionali

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**tot**
Abe 2016	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score matching)	* record linkage: objective outcomes	§ Not reported	* Subjects lost to follow up unlikely to introduce bias	**Good quality**
Aso 2017	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score matching)	* record linkage: objective outcomes	* Yes (28 days)	* Subjects lost to follow up unlikely to introduce bias (30-40% for BMI)	**Good quality**
Brenner 2018	* somewhat representative of the average population in the community	* drawn from the same community as the exposed cohort	* secure record	* yes	no control for confounding performed (similar baseline data)	* record linkage: objective outcomes	§ Not specified (longer than 24 hours)	§ Not reported	**Fair quality**
Dubose 2016	*	* drawn from the same community as the exposed cohort	* secure record	* yes	Unclear	* record linkage: objective outcomes	* Yes (24 h)	§ Not reported	**Good quality**
Garcia 2020	*	drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score	* record linkage: objective	§ Not reported	§ Not reported	**Fair quality**

					matching)	outcomes			
Inoue 2016	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score matching)	* record linkage: objective outcomes	§ Not reported	§ Not reported	**Good quality**
Joseph 2015	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score matching)	* record linkage: objective outcomes	* Yes (24-hour mortality, and mortality after 24 hours in both groups)	* Missing treated as missing completely at random.	**Good quality**
Moore 2015	*	* drawn from the same community as the exposed cohort	* secure record	* yes	no control for confounding performed however authors declared no differences between groups at baseline	* record linkage: objective outcomes	§ Not reported	§ Not reported	**Fair quality**
Matsumara 2017	*	* drawn from the same community as the exposed cohort	* secure record	* yes	no control for confounding performed	* record linkage: objective outcomes	Yes (24 hours,30 days)	§ Not reported	**Fair quality**
Nori 2015	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score matching)	* record linkage: objective outcomes	§ Not reported	* excluded patients with missing survival data	**Good quality**
Yamamoto 2019	*	* drawn from the same community as the exposed cohort	* secure record	* yes	* study controls for important factor (propensity score matching)	* record linkage: objective outcomes	Yes (28 days, 90 days)	* excluded patients with missing survival data	**Good quality**

§ Outcomes may have been influenced by time.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
    a) truly representative of the average population in the community *
    b) somewhat representative of the average population in the community *
    c) selected group of users eg nurses, volunteers
    d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
    a) drawn from the same community as the exposed cohort *
    b) drawn from a different source
    c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a) secure record (eg surgical records) *
    b) structured interview
    c) written self report
    d) no description
4) Demonstration that outcome of interest was not present at start of study
    a) yes *
    b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
    a) study controls for the most important factor*
    b) study controls for any additional factor *
    c) no control for confounding performed

Outcome

1) Assessment of outcome
    a) independent blind assessment *
    b) record linkage *
    c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) *

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for *

b) subjects lost to follow up unlikely to introduce bias - small number lost - >70 % follow up, or description provided of those lost) *

c) follow up rate <70% and no description of those lost

d) no statement

CQ7: Controllo dell'emorragia nel setting pre- e intraospedaliero: REBOA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REBOA	control (open surgery/no-REBOA)	Relative (95% CI)	Absolute (95% CI)		
Overall Crude Mortality-subgroup analysis												
11	observational studies	not serious	very serious [a]	serious [b]	serious [c]	none	1423/2317 (61.4%)	1776/3502 (50.7%)	**OR 0.68** (0.38 to 1.22)	**95 fewer per 1.000** (from 226 fewer to 49 more)	⨁◯◯◯ VERY LOW	CRITICAL
Overall Crude Mortality-subgroup analysis - vs open surgery												
5	observational studies	not serious	not serious	serious [b]	not serious	none	618/980 (63.1%)	577/677 (85.2%)	**OR 0.42** (0.32 to 0.54)	**144 fewer per 1.000** (from 204 fewer to 95 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Overall Crude Mortality-subgroup analysis - vs RT+REBOA												
1	observational studies	serious [d]	not serious	serious [b]	serious [e]	none	41/76 (53.9%)	27/30 (90.0%)	**OR 0.13** (0.04 to 0.47)	**361 fewer per 1.000** (from 635 fewer to 91 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Overall Crude Mortality-subgroup analysis - vs no-REBOA												
5	observational studies	not serious	serious [f]	serious [b]	not serious	none	764/1261 (60.6%)	1172/2795 (41.9%)	**OR 1.68** (1.03 to 2.72)	**129 more per 1.000** (from 7 more to 243 more)	⨁◯◯◯ VERY LOW	CRITICAL
Overall Adjusted Mortality-subgroup analysis												
8	observational studies	not serious	very serious [a]	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	1423/2317 (61.4%)	1776/3502 (50.7%)	**OR 0.87** (0.48 to 1.58)	**35 fewer per 1.000** (from 177 fewer to 112 more)	⨁◯◯◯ VERY LOW	CRITICAL
Overall Adjusted Mortality-subgroup analysis - vs open surgery												
5	observational studies	not serious	not serious	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect	618/980 (63.1%)	577/677 (85.2%)	**OR 0.38** (0.20 to 0.74)	**166 fewer per 1.000** (from 317 fewer to 42 fewer)	⨁⨁◯◯ LOW	CRITICAL
Overall Adjusted Mortality-subgroup analysis - vs RT+REBOA												
1	observational studies						41/76 (53.9%)	27/30 (90.0%)	not estimable		-	CRITICAL
Overall Adjusted Mortality-subgroup analysis - vs no-REBOA												
5	observational studies	not serious	very serious [a]	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect	764/1261 (60.6%)	1172/2795 (41.9%)	**OR 1.40** (0.79 to 2.46)	**83 more per 1.000** (from 56 fewer to 221 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REBOA	control (open surgery/no-REBOA)	Relative (95% CI)	Absolute (95% CI)		
adjusted mortality ED												
3	observational studies	not serious	very serious [a]	serious [b]	very serious [c]	all plausible residual confounding would reduce the demonstrated effect	248/1401 (17.7%)	196/1172 (16.7%)	**OR 0.80** (0.14 to 4.74)	**29 fewer per 1.000** (from 140 fewer to 320 more)	⨁◯◯◯ VERY LOW	CRITICAL
adjusted mortality 24 h												
2	observational studies	not serious	serious [f]	serious [b]	very serious [c]	all plausible residual confounding would reduce the demonstrated effect	70/186 (37.6%)	90/348 (25.9%)	**OR 1.00** (0.10 to 9.48)	**0 fewer per 1.000** (from 225 fewer to 509 more)	⨁◯◯◯ VERY LOW	CRITICAL
adjusted mortality 1 month												
2	observational studies	not serious	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	71/257 (27.6%)	93/397 (23.4%)	**OR 0.77** (0.36 to 1.61)	**44 fewer per 1.000** (from 135 fewer to 96 more)	⨁◯◯◯ VERY LOW	CRITICAL
Volume of blood components												
7	observational studies										⨁◯◯◯ VERY LOW	CRITICAL
Health related quality of Life												
4	observational studies										⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												
4	observational studies										⨁◯◯◯ VERY LOW	CRITICAL
Time of control hemmorage												
1	observational studies										⨁◯◯◯ VERY LOW	CRITICAL
Mortality 12 months												
0	observational studies										⨁◯◯◯ VERY LOW	IMPORTANT
Improvement in haemodynamic												
2	observational studies										⨁◯◯◯ VERY LOW	IMPORTANT
failure/success of REBOA technique												
2	observational studies										⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. I2>90%

b. variability of setting (no-prehospital)

c. Confidence intervals crossed the line of no difference with plausible effects in favor to the experimental group

d. risk of bias in outcome assessement and follow-up

e. number of events <200

f. I2>75%

Appendice F - Bibliografia degli studi inclusi

CQ7: Controllo dell'emorragia nel setting pre- e intraospedaliero: REBOA

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