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Effects on mortality of blood purification techniques in severe septic shock patients. An updated Bayesian network meta-analysis of randomized controlled trials

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ABSTRACT

Background: Sepsis is a very severe condition that carries a high risk of death. Blood purification methods have been employed alongside conventional treatment to help decrease the death rate associated with severe sepsis.
Research question: The objective of our network meta-analysis (NMA) was to determine the most efficient blood purification device for decreasing mortality in individuals with severe septic shock.
Study design and methods: The network meta-analysis (NMA), which incorporated randomized clinical trials (RCTs), was performed by modeling the binary outcome "mortality" utilizing a Bayesian hierarchical model. We examined direct comparisons of blood purification methods employed for the immediate management of individuals experiencing severe septic shock. The studies' risk of bias was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions. The main result was death rate. We calculated summary relative risks (RRs) through pairwise meta-analysis and NMA employing fixed effects. We utilized the surface beneath the cumulative ranking curve (SUCRA) to display the order of interventions.
Results: Out of 379 references, we incorporated 31 RCTs. We discovered 15 distinct treatment approaches. The overall count of patients was 2678. The forest plot, league heat table, and SUCRA plot indicated that the TORAYMYXIN™ filter (PMX) and HA 330™ were the sole devices that notably decreased mortality in comparison to standard treatment.
Interpretation: The PMX filter and HA 330 for blood purification greatly lower mortality rates in patients experiencing severe septic shock. All patients who received convection at any prescribed convective dose exhibited greater mortality compared to those receiving standard therapy.
PROSPERO (CRD42023486159).

1. Introduction

The Third International Consensus (Sepsis-3) defines sepsis as "organ dysfunction caused by a dysregulated host response to infection," underlining the crucial role of the immune response in the development of clinical sepsis [1]. Sepsis is a life-threatening condition caused by an excessive host response to infection that can lead to severe multiorgan dysfunction associated with high mortality.

Abbreviations: NMA, Network meta-analysis; ALT, Alteco cartridge.; PMX, Toraymyxin®; EFF, Efferon®; CPFA, Coupled plasma filtration adsorption (CPFA); HA330, HA330 cartridge; CYT, Cytosorb cartridge.; OXI, oXiris® filter.; iHSA, Immobilized human serum albumin with MATISSE®-adsorber.; PE, Plasma Exange.; CRRT with standard dose (25–30 ml/kg/h effluent), Standard volume continuous veno-venous hemofiltration. Ultrafiltrate volume between 25 and 35 ml/kg/h; HVCVVH, High volume continuous veno-venous hemofiltration. Ultrafiltrate volume between >35 ml/kg/h and < 60/ml/kg/h; VHVCVVH, Very high volume continuous veno-venous hemofiltration. Convective dose >60 ml/kg/h; PHVCVVH, Pulse high volume continuous veno-venous hemofiltration. Convective dose of 85 ml/kg/h; RCTs, Randomized controlled trials; CrIs, Credible intervals; MCMC, Markow Chain Monte Carlo; GLM, Generalized linear model; DIC, Deviance information Criterion; Dres, Mean of residual deviance; SUCRA, Surface Under Comparative Ranking Curve; LTH, League table heatmap; HA, Hemoadsorption; DAMPs, Damaged-associated molecular pattern; CS, Cytokine storm; HF, Hemofiltration.

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Furthermore, although mortality has been slowly decreasing in recent years, in patients with severe haemodynamic compromise, in-hospital mortality remains close to 60 % [2].

Over the last three decades, several studies have clarified the biochemical, immunological, and genetic mechanisms of sepsis. On the other hand, treatment options are still limited to the timely administration of fluids and early antibiotic therapy, which have not yet been demonstrated to be effective in reducing mortality [3]. Nevertheless, understanding the pathophysiologic mechanisms of sepsis (mainly the dysregulated cytokine response) has made other therapeutic tools available.

This led to the appealing idea that the removal of circulating cytokines could be a key point in improving organ dysfunction. Blood purification techniques (BPT) are based on the principle that modulating pro- and anti-inflammatory mediators or bacterial endotoxins could attenuate the sepsis-related systemic inflammatory response [4,5]. However, the effectiveness of these techniques has not yet been clearly demonstrated [6].

The aim of this network meta-analysis (NMA) was to assess the effectiveness of blood purification techniques in severe septic shock and to determine which of the available tools can be considered the most effective.

2. Study design and methods

To investigate whether blood purification techniques were effective in treating severe septic shock, a standard meta-analysis and Bayesian NMA were carried out. The endpoint was to determine whether one or more blood purification techniques could reduce mortality in patients with severe septic shock.

Different treatments were analyzed using statistical inference, combining direct and indirect estimates. The study protocol was registered in PROSPERO (CRD42023486159).

2.1. Eligibility criteria

This NMA included randomized controlled trials (RCTs) comparing blood purification techniques with standard treatment in adult patients with severe septic shock. Studies including patients with vasoplegic shock after cardiopulmonary bypass or COVID-19-related vasoplegic shock were excluded.

To evaluate the effects of BPT only in patients with high expected mortality, we included only studies in which the mean APACHE II score was greater than 25 (expected mortality 55 %) and the mean SOFA score was greater than 10 (expected mortality 40–60 %).

The primary outcome was in-hospital mortality.

2.2. Search strategy and study selection

Randomized controlled trials (RCTs) were identified through an electronic search of EMBASE, MEDLINE, Web of Science, and international registries for published and unpublished trials using a combination of MeSH terms and text words (e-Appendix 1). The literature search was last updated in December 2024.

Two researchers (MM, EG) conducted the electronic search separately and selected the papers considered worthy of inclusion. In case of a discrepancy between the two researchers, the selection committee (MM, EG, PZ, FN) convened to reach a final decision.

The systematic review was carried out in accordance with PRISMA recommendations (e-Appendix 2).

2.3. Study screening

2.3.1. Inclusion criteria

RCTs obtained from literature searches were first selected by checking the title and abstract. When a paper was deemed relevant to the study's objective, the full article was downloaded.

2.3.2. Exclusion criteria

Review studies, retrospective studies, observational studies, case reports, animal studies, studies conducted on children, duplicate reports, articles involving repeated experiments (commentary papers on specific studies or secondary analyses of experimental data), non-randomized trials, studies on post-cardiopulmonary bypass vasoplegic shock, and studies including patients with COVID-19 were excluded.

2.3.3. Risk of bias assessment

The risk of bias was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [7]. The overall risk of bias was categorized as low, high, or unclear. Heterogeneity among studies in direct comparisons was evaluated using Cochran's Q-test and the I^2 statistic by Higgins and Thompson [8]. The presence of effect modifiers attributable to heterogeneity was considered acceptable if the χ^2 *P*-value was >0.10.

2.4. Data analysis

The following data were examined: experimental design, study duration, country where the study was conducted, inclusion criteria, patient age and gender, detailed experimental procedures, type of blood purification device used, and outcomes.

Data extraction was performed using the PRISMA data extraction form (e-Appendix 2). Methodological details regarding internal validity, risk of bias assessment, statistical analysis, and the Bayesian NMA procedure are reported in the Supplemental Digital Content.

The different interventions were mapped onto a network graph, where node size was proportional to the number of studies, and edge thickness was proportional to the number of comparisons.

Mortality data from individual studies were analyzed to compute the risk ratio (RR) with 95 % credible intervals (CrIs), using the inverse variance method with either a fixed-effect or random-effects model.

The network analysis was conducted by modeling the binary outcome “mortality” using a Bayesian hierarchical model with the Markov Chain Monte Carlo (MCMC) approach.

A generalized linear model (GLM), including both fixed-effects and random-effects models, was constructed based on an a priori non-informative distribution, binomial likelihood distribution, and a log link function.

The indirect estimate was calculated as the difference between the corresponding direct estimates, and the 95 % CrI was obtained using normal approximation.

MCMC simulation was used to perform the meta-analysis, with a burn-in of 5000 iterations followed by 20,000 iterations, with a thinning factor of 1.

Statistical models were selected through a trial-and-error process based on MCMC convergence diagnostics (Gelman-Rubin trace plots and potential scale reduction factors) and the analysis of leverage plots. In the MCMC cycle, for each iteration, treatment regimens were ranked according to the estimated RR.

Leverage plots were analyzed by considering the distribution of observations, the number of effective parameters, model fit, and the Deviance Information Criterion (DIC).

A difference of >5 points in total residual deviance was used to detect substantial differences across different GLMs.

We selected either the fixed-effect or random-effects model by calculating the posterior mean of residual deviance (Dres) and DIC statistics. A compromise between accuracy and complexity (favoring a lower DIC) was the criterion for choosing the GLM models.

Standard therapy was used as the benchmark treatment. For each intervention, we synthesized summary estimates against standard therapy to generate an overall ranking of interventions.

We assessed the consistency of this network meta-analysis as

described in NICE-DSU TSD 4 [9]. The results were compared by fitting a Consistency model, which estimated only the effects between each studied treatment and the reference therapy (Standard therapy). The Inconsistency model was then used to derive indirect treatment effects through the Consistency equation.

The 95 % CrI was used to obtain accurate precision estimates.

All comparisons were summarized using a forest plot, Surface Under the Cumulative Ranking Curve (SUCRA), and a League Table Heatmap (LTH), with usual care as the reference treatment. These methods were used to present the hierarchy of interventions for each outcome.

All values represent the percentage of effectiveness achieved by each treatment relative to the most effective intervention.

The network meta-analysis was performed using the BUGSnet package in R [10] and Review Manager (RevMan) version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

3. Results

Out of 379 references identified, 31 RCTs [11–41] were included, with the selection process reported in the PRISMA flowchart (e-Fig. 1).

Fifteen different treatment strategies were identified. All studies, except one, were two-arm trials.

The total number of included patients was 2678, and the number of possible pairwise comparisons was 105. Seventeen pairwise comparisons included direct data. A total of 1209 patients died. No study included in the NMA had zero events.

Table 2 summarizes the characteristics of the studies. The technical features of each device are shown in Table 1. The characteristics of the studies are presented in Fig. 2. The network graph, shown in Fig. 1, was found to be connected.

e-Table 1, e-Table 2, and e-Table 3 provide the complete network characteristics. e-Fig. 2 illustrates the risk of bias within studies.

In 10 studies, the PMX (Toraymyxin™) filter was used, while in 8 studies, standard-volume continuous venovenous hemofiltration (CRRT with standard dose (25–30 ml/kg/h effluent)) was employed. In 5 studies, very-high-volume continuous venovenous hemofiltration (VHVCVVH) was used, while in 3 studies, coupled plasma filtration adsorption (CPFA) was applied.

The HA330™ (HA330) and high-volume continuous venovenous hemofiltration (HVCVVH) were used in 2 studies. Finally, all other devices were used in a single study.

Except for pulse very-high-volume continuous venovenous hemofiltration (PHVCVVH) and intermittent hemodialysis (IHD), all systems were studied in at least one standard therapy-controlled trial.

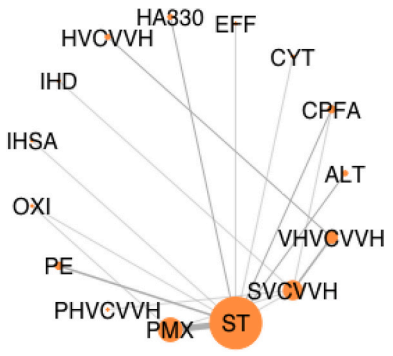

Fig. 1. Network plot of different treatments. ST: standard therapy, PMX: Toraymixyn, ALT: Alteco, EFF: Efferon, CPFA: coupled plasma filtration adsorption, CYT: Cytosorb, OXI: oXiris, PE: plasma exchange, HA330: HA330, CRRT with standard dose (25–30 ml/kg/h effluent): standard volume continuous veno-venous hemofiltration, HVCVVH: high volume continuous veno-venous hemofiltration, VHVCVVH: very high volume continuous veno-venous hemofiltration, iHSA: immobilized human serum albumin, IH: intermittent hemodialysis.

Table 1
Devices characteristics.

Device	Characteristics	Mechanism of action
ALT	Alteco cartridge. Syntetic polypeptide bound to porous polyethylene discs. 2–6 h. One session is usually sufficient to achieve improvement. Preated procedures can be performed. Blood flow rate 150 ml/min. Anticoagulation: heparin	Selective hemoadsorption
PMX	Toraymyxin® Polymixyn B-immobilized fiber blood-purification column. 2-h session daily for 2 consecutive days. Blood flow rate 80–120 ml/min. Anticoagulation: Heparin	Selective hemoadsorption
EFF	Efferon LPS The polymeric matrix of the sorbent consisted of macroporous hypercrosslinked polystyrene beads with a large specific surface area of 700 to 900 m2/g. The duration of hemoadsorption 4 h performed twice at 24 h interval. Blood flow rate of 100 to 160 ml/min. Anticoagulation: heparin.	Unselective hemoadsorption
CPFA	Coupled plasma filtration adsorption (CPFA) is a detoxification system that combines a plasma adsorption circuit with a continuous renal replacement therapy. The CPFA circuit consists of a Micropes™ plasmafilter (0.45 m^2) in series with a high permeability polyphenylene haemofilter (Kuf 41 ml/h/mmHg, surface area 1.4 m^2). The plasma flow rate is 30–40 ml/min and the plasma passes into the sorbent adsorption cartridge. The cartridge contains a 70-g styrenic polymer resin. The resin is composed of mesoporous beads; the bead size is 50–100 μm; the average pore diameter is 30 nm and the surface area is 700 m^2/g = 50,000 m^2. Anticoagulation: heparin or citrate	Combined hemoadsorption and hemofiltration
HA330	Styrene divinylbenzene copolymers. 2–6 h daily for 2 days. Blood flow rate up to 700 ml/min. Anticoagulation: heparin or citrate	Unselective hemoadsorption
CYT	Cytosorb cartridge. Porous polymer beads. Up to 24-h therapy daily for 2–7 consecutive days. Blood flow up to 700 ml/min. Anticoagulation:heparin or citrate	Unselective hemoadsorption
OXI	oXiris® filter. AN69-based membrane, surface treated with PEI and grafted with heparin. Prescribed dose>35 ml/kg/h (60 % convective). Filter replacement after 24 h or if there is no reduction in vasopressors dose by 50 %. Treatment should be stopped if vasopressors are reduced by >50 % or after 3 days of treatment in case of no-response. Blood flow 100–450 ml/min. Anticoagulation: heparin	Combined hemoadsorption and hemofiltration
iHSA	Immobilized human serum albumin with MATISSE®-	Unselective hemoadsorption

(continued on next page)

Table 1 (*continued*)

Device	Characteristics	Mechanism of action
	adsorber based on microporous beads immobilized by human serum albumin. Treatment dose 1.5 times of the estimated blood volume of the patient over 3–4 h	
PE	The plasma is separated from the corpuscular components of the blood by centrifugation, membrane filtration, or both. Can operate with a continuous or an intermittent flow. It is usually performed with centrifugal systems	
	the preferred devices are membrane-based (mTPE), including multifunctional renal replacement therapy (RRT) machines. The cell-rich blood that remains after plasma removal is mixed with the replacement fluid (e.g., albumin, plasma, or crystalloid) and returns to the patient to prevent hypovolemia. To reduce costs and donor exposures, up to 30 % of the replacement fluid may be a suitable crystalloid. Anticoagulation: heparin or citrate	
CRRT with standard dose (25–30 ml/kg/h effluent)	Standard volume continuous veno-venous hemofiltration. Ultrafiltrate volume between 25 and 35 ml/kg/h	Hemofiltration
HVCVVH	High volume continuous veno-venous hemofiltration. Ultrafiltrate volume between >35 ml/kg/h and < 60/ml/kg/h	Hemofiltration
VHVCVVH	Very high volume continuous veno-venous hemofiltration. Convective dose >60 ml/kg/h	Hemfiltration
PHVCVVH	Pulse high volume continuous veno-venous hemofiltration. Convective dose of 85 ml/kg/h for the first 6 h, followed by a volume of 35 ml/kg/h for 18 h	Hemofiltration

Detailed results of pairwise meta-analyses are presented in the Supplemental Digital Content (e-Fig. 3, e-Fig. 4, e-Fig. 5, e-Fig. 6, e-Fig. 7, e-Fig. 8, e-Fig. 9).

Only one pairwise meta-analysis showed significant heterogeneity: the comparison between PMX filter and standard therapy (e-Fig. 4).

Covariate analysis revealed that in the comparison between PMX and standard therapy, the effect of PMX differed between younger patients (<65 years) and elderly patients (>65 years). This difference could explain the heterogeneity observed in the direct comparison.

We assessed DIC and produced a leverage plot (Fig. 2). We compared the fit of both fixed- and random-effects models, and the fixed-effects model was preferred due to its lower DIC value and the presence of fewer outliers in the leverage plot.

To assess the presence of inconsistency, we fitted an NMA model, obtaining leverage plots by comparing a random-effects inconsistency model with a random-effects consistency model. The DIC for the consistency model was marginally lower than that of the inconsistency model.

When evaluating the fit of both models, DIC values were the same, with similar leverage plots, and the posterior mean of the residual deviance showed comparable values in both models. Given its adequate fit and parsimony, the consistency model was preferred (Fig. 3).

A plot of the posterior mean deviance of individual data points in the inconsistency model against their posterior mean deviance in the consistency model showed that, except for two points, the data aligned closely with the y = x line, indicating general agreement between the two models (Fig. 3).

We considered the Fixed-Effects Model the most appropriate for describing the NMA results, as it had a lower DIC and fewer outliers than the Random-Effects Model.

As visualized in the SUCRA plot (e-Fig. 9), LTH (Fig. 4), and FP (Fig. 4), ALT, HA330, plasma exchange (PE), and PMX curves were consistently above other treatment curves, suggesting they were the most beneficial interventions in terms of mortality reduction.

Analysis of the forest plot provided interesting evidence: ALT, EFFE, HA330, and PMX all had a RR lower than 1compared to standard therapy.

Analysis of the LTH determined which techniques were significantly able to reduce mortality. The results showed that only PMX (RR 0.83; 95 % CrI 0.23–3.93) and HA330 (RR 0.62; 95 % CrI 0.20–3.13) significantly reduced mortality compared to standard therapy.

Another important finding from the forest plot was that all hemodiafiltration techniques and CYT had a relative risk greater than 1, with only CRRT with standard dose (25–30 ml/kg/h effluent) (RR 1.50; 95 % CrI 0.51–7.4) appearing to significantly increase mortality compared to standard therapy.

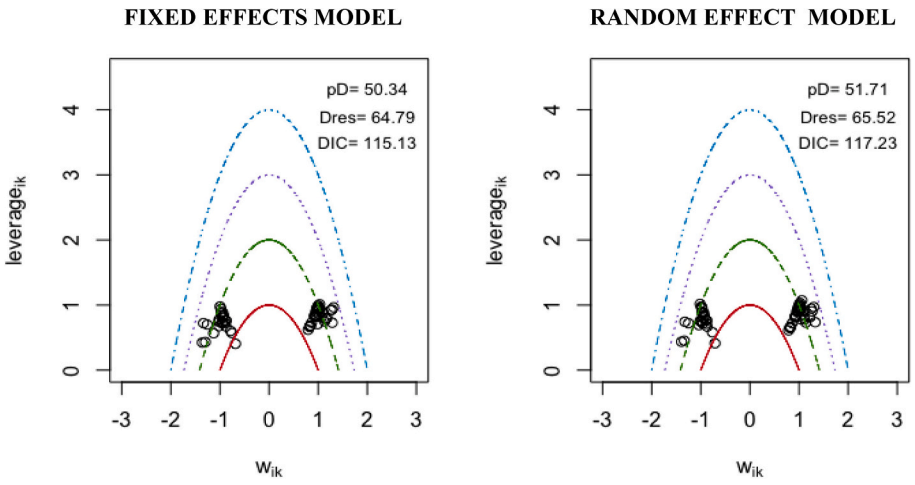

Fig. 2. Leverage plots and fit statistics. We compared the fit of both fixed- and random-effects model. According to a visual examination of the leverage plots and the comparison of the DIC values, the fixed effect model was preferred over the random effect model because the DIC value is lower.

Table 2
Study characteristics.

Study	Arm	Pathogen	Intervention	Comparison	Number	SCORE
1 Boussekey 2008	2	NR	Very High Volume CVVH	Standard Volume CVVH	19	APACHE II:31
2 Busund 2001	2	NR	Plasma Exchange	Standard Therapy	106	APACHE III: 56
3 Chu 2020	2	NR	HA330 + Pulse High Volume	Standard Volume CVVH	30	APACHE II: 22
4 Coudroy 2017	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	213	SAPS II:29
5 Cruz 2009	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	64	APACHE II: 20
6 Dellinger 2018	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	450	APACHE II: 28
7 Gimenez-Esparza 2019	2	NR	CPFA	Standard Therapy	49	APACHE II: 27
8 Hassan 2013	2	NR	CPFA	Standard volume CVVH	23	APACHE II: 21
9 Huang 2010	2	Mixed	HA 330	Standard Therapy	44	APACHE II: 28
10 Hawchar 2019	2	Mixed	Cytosorb	Standard Therapy	20	APACHE II: 28
11 Joannes-Boyau 2013	2	Mixed	Very high Volume CVVH	Standard Volume CVVH	137	SOFA: 12
12 John 2001	2	Mixed	Standard Volume CVVH	Standard Therapy	30	APACHE II: 33
13 Lipcsey 2020	2	Mixed	ALTECO filter	Standard Therapy	15	SOFA: 13
14 Livigni 2014	2	Mixed	CPFA	Standard Therapy	184	SOFA: 10
15 Nakamura 1999	2	GNB	Polymyxin Hemoperfusion	Standard Therapy	50	APACHE II: 23
16 Nakamura 2002 (CIC)	2	GNB	Polymyxin Hemoperfusion	Standard Therapy	120	APACHE II: 23
17 Nakamura 2004 (ICM)	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	25	APACHE II: 28
18 Park 2016	2	Mixed	Very High Volume CVVH	High Volume CVVH	212	APACHE II: 28
19 Payen 2009	2	Mixed	Standard Volume CVVH	Standard Therapy	76	SOFA: 11
20 Payen 2015	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	232	SOFA: 10
21 Quenot 2015	2	Mixed	Very High Volume CVVH	Standard Therapy	60	SOFA: 12
22 Reeves 1999	2	Mixed	Plasma Exchange	Standard Therapy	22	APACHE II: 25
23 Rey 2023	2	Mixed	Efferon Hemoperfusion	Standard Therapy	58	APACHE II: 24
24 Reinhart 2004	2	GNB	IHSA	Standard Therapy	140	APACHE II: 28
25 Schadler 2017	2	Mixed	Cytosorb	Standard Therapy	97	APACHE II: 24
26 Stahl 2022	2	Mixed	Plasma Exchange	Standard Therapy	40	SOFA: 16
27 Shum 2014	2	Mixed	ALTECO filter	Standard Therapy	15	SOFA: 14
28 Srisawat 2018	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	59	SOFA: 13
29 Suzuki 2002	2	Mixed	Polymyxin Hemoperfusion	Standard Therapy	48	APACHE II: 25
30 Zhang 2012	2	Mixed	Very High Volume CVVH	High Volume CVVH	280	APACHE II: 22
31Wendel-Garcia 2023	3	Mixed	Oxiris or Toraynixyn	Standard Therapy	30	SOFA: 13

Abbreviations: CVVH continuous veno-venous hemofiltration.

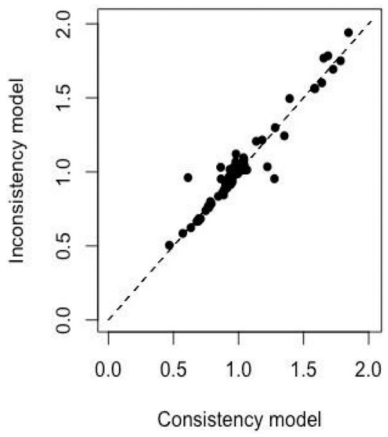

Fig. 3. Posterior mean deviance comparison plot. Each data point represents a treatment arm's contribution to posterior mean deviance for the consistency model (horizontal axis) and the inconsistency model (vertical axis).

4. Discussion

Our NMA clearly shows that PMX and HA330 use, compared with standard therapy, is associated with a significant reduction in mortality in patients with severe septic shock.

To our knowledge, this is the first study demonstrating that high-volume hemofiltration (HVHF)-based purification techniques not only fail to reduce mortality in patients with severe septic shock but may actually increase it compared to standard therapy.

The use of blood purification is a logical therapeutic approach, based on scientific evidence that septic shock is not directly caused by the infectious agent but rather by an exaggerated host immune response.

The first event in an infectious process is pathogen recognition by the immune system. This triggers lymphocyte activation and the massive synthesis of pro- and anti-inflammatory cytokines (*cytokine storm* CS), which leads to organ dysfunction. Damaged cells express damage-associated molecular patterns (DAMPs) on their surface, which are then released into the bloodstream and recognized by pattern recognition receptors, perpetuating a vicious cycle. After the initial CS, a state of immunoparalysis occurs, which plays a fundamental role in sepsis-related mortality [42,43].

The first blood purification technique used was hemofiltration (HF), aimed at removing cytokines from circulation to counteract CS. The next step was to increase the refusion rate to maximize cytokine removal [44].

Therapies such as high-volume hemofiltration and high-cutoff membrane filtration may increase inflammatory cytokine clearance. However, cytokine and ligand removal from the bloodstream can affect immune responses and impair metabolic adaptation in sepsis [45]. High-volume hemofiltration removes both pro- and anti-inflammatory cytokines, potentially disrupting immune system balance.

Despite promising results in animal models, clinical trials in humans have produced conflicting findings [46,47]. Given this evidence, the development of new and more effective blood purification technologies is highly desirable.

4.1.1. *Hemoadsorption (HA)*

Hemoadsorption (HA) involves direct contact between blood and sorbents in an extracorporeal circuit. The sorbents attract solutes through hydrophobic interactions, ionic attraction, hydrogen bonding, and van der Waals interactions [48].

The key advantage of HA is its high-molecular-weight adsorption potential, allowing it to target large molecules.

During hemoadsorption, solute removal depends on perfusion rates

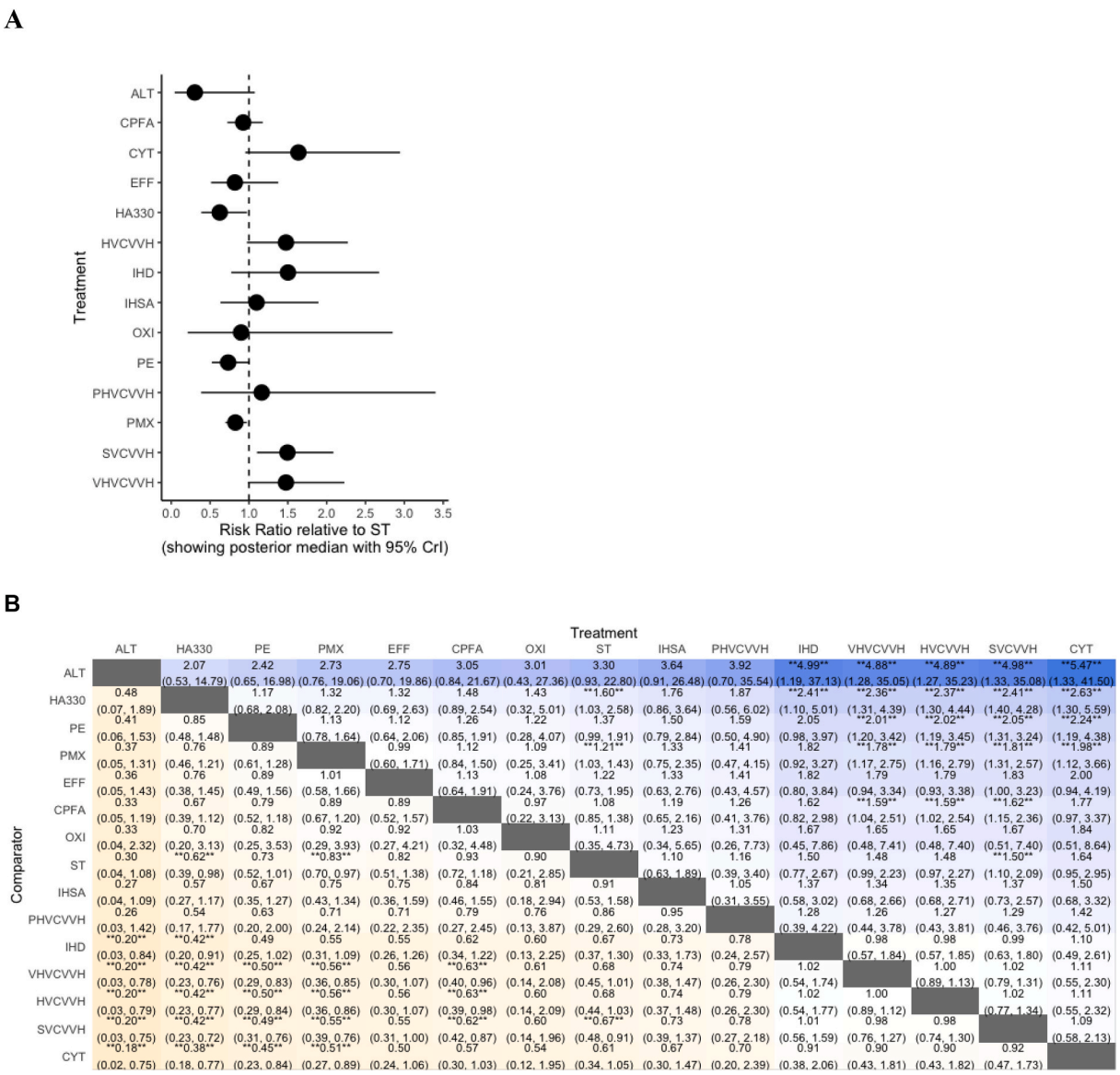

Fig. 4. **A**) Forrest plot of effect of each treatment respect to standard treatment. **B)** League Table Heatmap. The values in each cell represent the relative treatment effect (and 95 % credible intervals) of treatment on the top, compared to the treatment on the left. A double asterisk indicates statistical significance.

and membrane characteristics, achieved through binding molecules to adsorbent materials [49]. Sorbent-based devices have large surface areas and high biocompatibility, ensuring efficient removal of middle- to high-molecular-weight solutes [50].

4.1.2. Polymyxin B (PMX)

The most extensively studied hemoadsorption device is Polymyxin B [51]. Polymyxin B is a cyclic basic polypeptide that disrupts Gram-negative bacterial cell membranes. Polymyxin B-immobilized polystyrene-derived fibers are used to remove endotoxins from the bloodstream.

In the multicenter RCT EUPHAS (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis), 64 patients with abdominal severe sepsis or septic shock were randomized to either conventional therapy or conventional therapy plus PMX.

The study was interrupted, as it was deemed unethical to withhold this therapy [15].

4.1.3. HA330 Hemoadsorption

The use of HA330 hemoadsorption in septic shock has attracted significant attention in recent clinical research, highlighting its potential to reduce inflammatory mediators and improve patient outcomes.

The HA330 cartridge is designed to remove pro-inflammatory cytokines and harmful substances from the bloodstream, thereby addressing the underlying pathophysiology of septic shock.

Recent studies have shown that HA330 can lead to a marked reduction in inflammatory markers. For example, Onuk et al. [52] reported that HA330, significantly reduced white blood cell counts, neutrophil counts, C-reactive protein (CRP), and procalcitonin levels.

Similarly, Kaçar et al. [53] found that HA330 hemoadsorption reduced Sequential Organ Failure Assessment (SOFA) scores, indicating improved organ function in critically ill patients.

The safety profile of HA330 has also been a focus of research. Sazonov et al. [54] conducted a case series in pediatric patients with cancer and septic shock, reporting that HA330 hemoadsorption reduced inflammatory mediators and led to clinical improvement without significant adverse effects.

4.2. Limitations

1. Mortality as the Primary Outcome
   While we believe that mortality is the most reliable measure of treatment effectiveness, some authors argue that cytokine removal in sepsis is not primarily aimed at reducing mortality but rather serves as an adjunctive therapy when standard care alone fails to stabilize patients [55].
2. Quality of Included Trials
   The validity of our results is influenced by the quality of the included trials. In particular, small-sample trials are more susceptible to sampling errors, introducing imprecision into comparisons [56].
3. SUCRA and Treatment Ranking
   In network meta-analysis, SUCRA scores and rankograms are commonly used to compare treatment efficacy. However, these rankings are highly sensitive to small changes and have limited precision [57].
4. Limited Head-to-Head RCTs
   Our NMA includes relatively few direct head-to-head RCTs. Some trials also had an unclear risk of bias, primarily due to the absence of reported trial protocols.
5. Limited Data on the Oxiris™ Filter
   We included only a few studies evaluating the Oxiris™ filter, due to the scarcity of RCTs. However, non-RCT studies suggest that Oxiris™ may be highly effective in septic shock management.

5. Conclusions

Despite the limitations of this study, our findings suggest that PMX and HA330 hemoadsorption are the most effective blood purification devices for reducing mortality in patients with severe septic shock.

Conversely, patients treated with ultrafiltration, regardless of the refusion dose, had a relative risk (RR) greater than 1 compared to patients receiving standard therapy, indicating potential harm rather than benefit.

CRediT authorship contribution statement

Massimo Meco: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Emiliano Agosteo:** Writing – review & editing, Conceptualization. **Pierluigi Zulli:** Investigation, Data curation. **Fulvio Nisi:** Investigation, Data curation. **Enrico Giustiniano:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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