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Blood Purification for Adult Patients With Severe Infection or Sepsis/Septic Shock: A Network Meta-Analysis of Randomized Controlled Trials

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OBJECTIVES: This study aimed to conduct a comprehensive and updated systematic review with network meta-analysis (NMA) to assess the outcome benefits of various blood purification modalities for adult patients with severe infection or sepsis.

DATA SOURCES: We conducted a search of PubMed, MEDLINE, clinical trial registries, Cochrane Library, and Embase databases with no language restrictions.

STUDY SELECTION: Only randomized controlled trials (RCTs) were selected.

DATA EXTRACTION: The primary outcome was overall mortality. The secondary outcomes were the length of mechanical ventilation (MV) days and ICU stay, incidence of acute kidney injury (AKI), and kidney replacement therapy requirement.

DATA SYNTHESIS: We included a total of 60 RCTs with 4,595 participants, comparing 16 blood purification modalities with 17 interventions. Polymyxin-B hemoperfusion (relative risk [RR]: 0.70; 95% CI, 0.57–0.86) and plasma exchange (RR: 0.61; 95% CI, 0.42–0.91) were associated with low mortality (very low and low certainty of evidence, respectively). Because of the presence of high clinical heterogeneity and intransitivity, the potential benefit of polymyxin-B hemoperfusion remained inconclusive. The analysis of secondary outcomes was limited by the scarcity of available studies. HA330 with high-volume continuous venovenous hemofiltration (CVVH), HA330, and standard-volume CVVH were associated with shorter ICU stay. HA330 with high-volume CVVH, HA330, and standard-volume CVVH were beneficial in reducing MV days. None of the interventions showed a significant reduction in the incidence of AKI or the need for kidney replacement therapy.

CONCLUSIONS: Our NMA suggests that plasma exchange and polymyxin-B hemoperfusion may provide potential benefits for adult patients with severe infection or sepsis/septic shock when compared with standard care alone, but most comparisons were based on low or very low certainty evidence. The therapeutic effect of polymyxin-B hemoperfusion remains uncertain. Further RCTs are required to identify the specific patient population that may benefit from extracorporeal blood purification.

KEY WORDS: blood purification; cytokine; endotoxemia; network meta-analysis; sepsis

Sepsis is a major cause of mortality in critically ill patients, particularly those who develop multiple organ dysfunction syndrome (MODS) (1). Despite standard sepsis management, mortality and morbidity of septic shock remain high (2, 3), highlighting the need for investigation of new strategies to improve survival.

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KEY POINTS

Question: Do different extracorporeal blood purification modalities offer benefits for adult critical illness patients with severe infection or sepsis/septic shock? The study aimed to evaluate these benefits through network meta-analysis.

Finding: We analyzed 16 blood purification modalities with 17 interventions. Polymyxin-B hemoperfusion and plasma exchange, compared with standard care, were associated with lower mortality risk. The potential benefit of polymyxin-B hemoperfusion remained uncertain because of the presence of high clinical heterogeneity and intransitivity.

Meaning: Polymyxin-B hemoperfusion and plasma exchange may be potentially effective blood purification modalities but the evidence remain inconclusive. Further trials are needed to explore the optimal modalities for these patients.

Excessive cytokine production can cause sepsis-related MODS (4–7). Although blocking inflammatory mediators in animals has shown promising results (8), human trials on single cytokine blockage have not confirmed the benefits (9). However, extracorporeal blood purification may be a solution to break the vicious cycle by nonspecifically removing excessive cytokines and endotoxemia.

The recent guidelines and meta-analysis (2, 3, 10, 11) suggested against routinely using polymyxin-B hemoperfusion and the recommendation to apply other extracorporeal blood purification modalities was inconclusive. The evidence for extracorporeal blood purification in sepsis should be re-evaluated because new trials, including novel strategies, have been published. Furthermore, these modalities to decrease ICU length of stay (LOS), occurrence rate of acute kidney injury (AKI), and the need for organ support have not been systematically evaluated (10, 12–14). In this study, we conducted an updated systematic review to examine the benefits of different extracorporeal blood purification modalities in patients with severe infection or sepsis/septic shock via a network meta-analysis (NMA).

MATERIALS AND METHODS

Literature Search Strategy

The current study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for NMAs (**Supplementary Table 1**, http://links.lww.com/CCM/H375) and the protocol was registered in PROSPERO (CRD42022362318).

Two investigators (J.J.C., T.H.L.) conducted a search independently for studies published before September 26, 2022, in the databases of PubMed, MEDLINE, Cochrane Library (including ClinicalTrials.gov and International Clinical Trials Registry Platform) and the Embase without language limitation. We also screened for relevant trials and the references of review articles.

Study Eligibility and Excluding Criteria

Studies were enrolled if they met the following criteria: 1) population: critically ill adults with severe infection or sepsis/septic shock; 2) intervention: any extracorporeal blood purification modality for cytokine or endotoxin removal compared with other modalities or standard sepsis care; and 3) outcome: studies reported any of the primary outcome or secondary outcomes (details in the section of Outcome Measures). Only randomized controlled trials (RCTs) with parallel group design were included.

Studies were excluded if they did not report the outcome of interest, lacked detailed information on blood purification or hemofiltration strategies which impeded us from allocating them to the intervention groups, or focused on children.

The titles and abstracts of references found by the search process were initially independently screened by two investigators (J.J.C., T.H.L.) to exclude clearly irrelevant studies. Full texts of relevant articles were obtained to determine whether the studies are eligible. A third investigator (Y.T.H.) was consulted to resolve disagreements on eligibility and categorization of studies.

Data Extraction

Two investigators (J.J.C. and T.H.L.) extracted relevant information from each selected study independently. Data on study characteristics, enrolled participant demographics (age and gender, critical

illness severity [Sequential Organ Failure Assessment Score, SOFA Score; Acute Physiology and Chronic Health Evaluation II Score, APACHE II Score]), extracorporeal blood purification modality, source of infection and pathogen, AKI status, and endotoxemia status (endotoxin activity assay [EAA]) were extracted.

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Outcome Measures

The primary endpoint was overall mortality, and the 28-day or 30-day mortality was used as a priority for analysis. If 28-day or 30-day mortality was unavailable, we extracted data in the following sequence: in-hospital mortality, 60-day mortality, and 90-day mortality. If studies only reported mortality without identified duration or follow-up duration of less than 28 days, we regarded it as in-hospital mortality during analysis. The secondary outcomes were AKI occurrence rate, requirement of kidney replacement therapy, LOS in ICU (d), and length of mechanical ventilation (MV) (d). When analyzing the risk of kidney replacement therapy and AKI, blood purification modalities that could interfere with creatinine levels or kidney replacement therapy modalities themselves were not included. Examples of these modalities are plasma exchange (15) and continuous venovenous hemofiltration (CVVH).

Statistical Analysis

As for the evaluation of the effects of different extracorporeal blood purification modalities on mortality, AKI occurrence rate, and kidney replacement therapy requirement, risk ratios (RRs) were chosen. As for the evaluation of the effects on LOS in ICU and MV days, mean difference (MD) was used. Frequentist NMA with a random-effects model was performed via the netmeta package in R, version 4.0.2 (R Core Team, Vienna, Austria). Heterogeneity was examined using I^2, and small study bias was assessed by the funnel plot with Egger's test. Results from NMA and direct comparisons were summarized by a league table. The P-score method was used to measure the probability that a potentially effective extracorporeal blood purification modality was superior to a competing modality. Incoherence was evaluated by design-by-treatment interaction test and node splitting analysis (16, 17). A p value of greater than 0.1 indicated no concern regarding incoherence. We conducted sensitivity analyses for studies recruiting cases with clearly defined sepsis or septic shock, or published after 2013. We also performed subgroup analysis based on mortality rates of comparators (≥ 70% and < 70%) (also see **Supplementary Document 1**, http://links.lww.com/CCM/H375). Two modalities that showed potential for reducing mortality were further examined through additional sensitivity analysis and trial sequence analysis within the pairwise meta-analysis framework.

Risk-of-Bias and Quality Assessments

Risk-of-bias (RoB) was assessed by the Revised Cochrane RoB tool (18). Two independent reviewers (P.C.L. and Y.T.H.) assessed the RoB and in the case of any disagreement, a third reviewer (J.J.C.) was consulted to reach a decision. The certainty of evidence of the primary endpoint, overall mortality, was assessed by the Grading of Recommendations, Assessment, Development and Evaluation framework for NMA (19).

RESULTS

Study Selection

The search process and list of excluded studies are provided (**Supplementary Tables 2** and **3**, http://links.lww.com/CCM/H375). After eliminating duplicates, 882 references were screened based on their title or abstract, and 105 of these were retrieved as full texts. An additional 12 relevant references were found by reviewing references from meta-analyses or review articles, and 6 of these were included in the current meta-analysis. Twenty-three registered clinical trials were also examined to identify any published articles or results (**Supplementary Table 4**, http://links.lww.com/CCM/H375). Finally, 60 publications met the eligibility criteria (**Fig. 1**).

Classification of Extracorporeal Blood Purification Modalities and Study Characteristics

A total of 17 interventions, including 16 extracorporeal blood purification modalities (including 3 modalities combination regimens) and standard sepsis care, were identified (**Table 1**): 1) Alteco LPS Adsorber (Alteco Medical AB, Sweden), 2) coupled plasma filtration and adsorption hemofiltration (CPFA, consisted of MicropesTM plasmafilter and polyphenylene hemodialyzer, Lynda, Bellco, Mirandola, Italy),

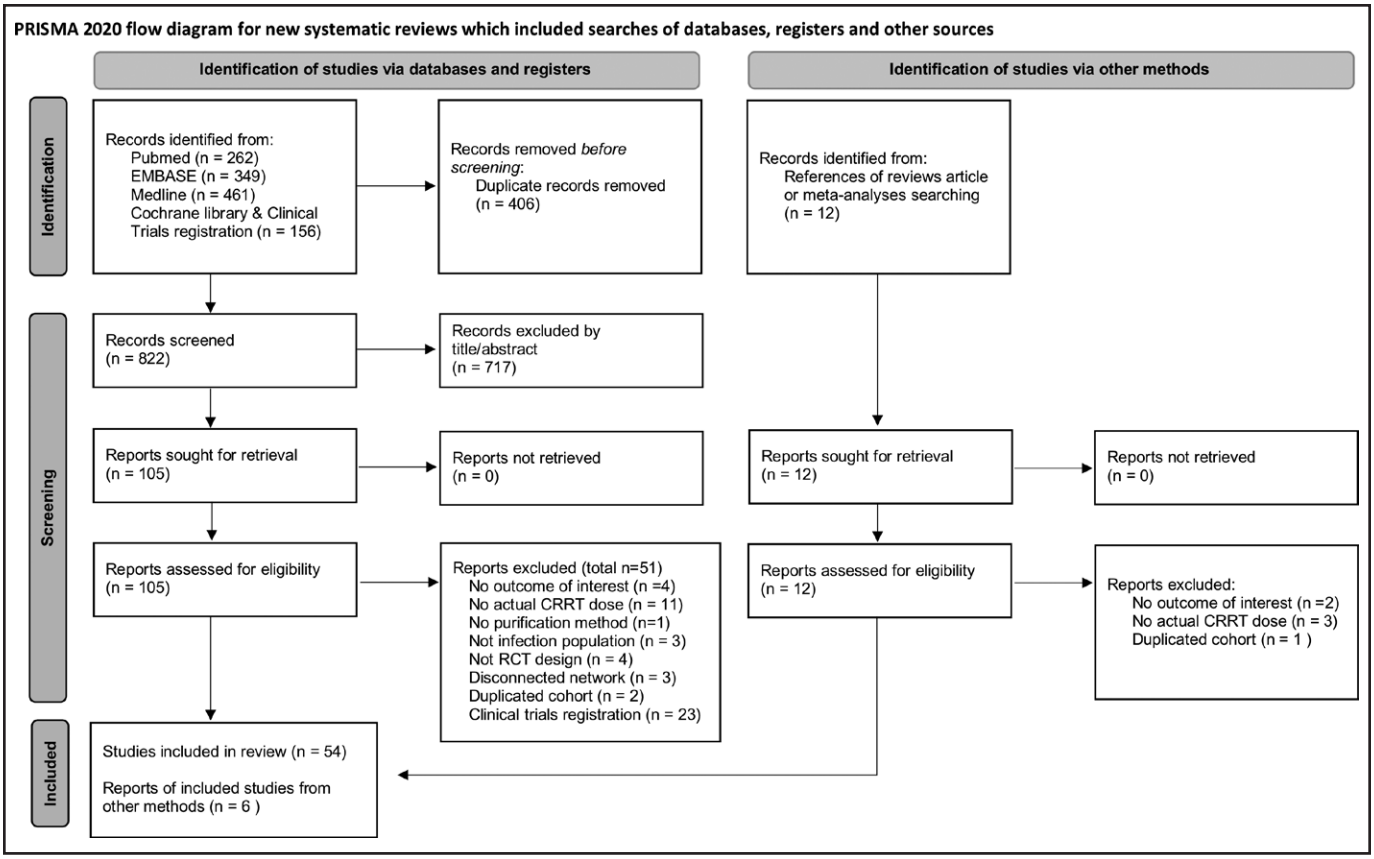

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. CRRT = continuous renal replacement therapy, RCT = randomized controlled trial.

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3) CytoSorb (CytoSorbents Europe GmbH, Germany), 4) HA330 hemoperfusion (Jafron Biomedical Co., Ltd., China), 5) immobilized human serum albumin (iHSA) (Fresenius HemoCare Adsorber Technology GmbH, Germany), 6) oXiris (Baxter, Deerfield, IL), 7) plasma exchange, 8) polymyxin-B hemoperfusion (TORAYMYXIN PMX, Toray industries, Tokyo, Japan), 9) standard-volume CVVH, 10) high-volume CVVH, 11) very high-volume CVVH, 12) pulse high-volume CVVH, 13) CPFA + standard-volume CVVH, 14) HA330 + high-volume CVVH, 15) HA330+pulse high-volume CVVH, and 16) selective cytopheretic device (SCD).

The characteristics of each study and their participants are provided (**Supplementary Table 5**, http://links.lww.com/CCM/H375). A total of 4,594 patients were included from 60 RCTs published from 1999 to 2022 (12–14, 20–76). The studies included participants with a mean or median age ranging from 33.2 to 74.9 years, mostly male (63.8%), APACHE II scores ranging from 17.1 to 34, and SOFA scores ranging from 5.6 to 16.5. Only 3 of the 60 enrolled trials set specific endotoxemia levels as part of enrolled criteria (EAA > 0.6 units) (12, 29, 65) (detailed characteristics are shown in **Supplementary Document 2**, http://links.lww.com/CCM/H375).

Primary Outcome

Figure 2*A* illustrates the network plot of 17 intervention arms involving 4,458 participants from 58 RCTs, which compared the effectiveness of extracorporeal blood purification modalities to reduce mortality in adult patients with severe infection. In this NMA, polymyxin-B hemoperfusion (RR: 0.70; 95% CI, 0.58–0.86; P score 0.58) and plasma exchange (RR: 0.61; 95% CI, 0.42–0.91; P score 0.67) were associated with lower RR for mortality compared with standard care (**Fig. 2*B*; Supplementary Tables 6** and **7**, http://links.lww.com/CCM/H375). Moderate heterogeneity (I^2 = 43.7%; 95% CI, 19.1–60.9%) was observed, and potential publication bias was detected (p = 0.01) (**Supplementary Fig. 1**, http://links.lww.com/CCM/H375). The certainty of evidence of 16 interventions is summarized in **Table 2**. Most interventions (14/16) had a very low

TABLE 1.
Classification, Nomenclature of Extracorporeal Blood Purification Modalities

Abbrevation	Extracorporeal Blood Purification Technique
Alteco	The Alteco lipopolysaccharides adsorber was used for hemoperfusion sessions lasting 2–6 hr each, with a total of two sessions
CPFA	Coupled plasma filtration and adsorption (CPFA) involved the treatment of more than 0.2 L/kg or 10 L of plasma per day through a series of 3–5 sessions
CytoSorb	CytoSorb was incorporated into the continuous venovenous hemodialysis/hemodialysis circuit, extracorporeal membrane oxygenation system, or cardiopulmonary bypass system during surgical procedures
HA330	HA330 adsorbent, a neutro-macroporous resin column used for hemoadsorption, was administered alone for 2 hr of hemoperfusion over a period of 3 d. It could also be used in combination with continuous kidney replacement therapy (CKRT)
iHSA	Treatment involved immobilized human serum albumin (iHSA) Fresenius Matisse EN 500 endotoxin adsorber and a Fresenius Hemoadsorption Machine 4008 ADS (treatment dose was 1.5 times of the estimated blood volume of the patient over 3–4 hr)
oXiris	oXiris is a modified hemodiafilter/hemoabsorber with a heparin-coated design that was integrated into the CKRT circuit
Plasma exchange	Plasma exchange was performed either with a fixed volume (12 units of plasma, 2,000 mL) or calculated based on body weight (30–40 to 100 mL/kg) for each session
Polymyxin-B	Polymyxin-B hemoperfusion using Toraymyxin was conducted according to the most commonly used protocol, which involved 2 sessions administered on 2 consecutive days, with each session lasting 2 hr
Standard-volume CVVH	Standard-volume continuous venovenous hemofiltration was performed with an ultrafiltrate volume ranging between 25 and 35 mL/kg/hr
High-volume CVVH	High-volume continuous venovenous hemofiltration was conducted with an ultrafiltrate volume ranging between > 35 and 60 mL/kg/hr
Very high-volume CVVH	Very high-volume continuous venovenous hemofiltration was performed with an ultrafiltrate volume exceeding 60 mL/kg/hr
Pulse high-volume CVVH	Continuous venovenous hemofiltration was conducted with an initial ultrafiltrate volume of 85 mL/kg/hr for 6 hr, followed by a reduced ultrafiltrate volume of 35 mL/kg/hr for the subsequent 18 hr
SCD	Selective cytopheretic device (SCD) with synthetic membrane cartridges with immunomodulatory effects could deactivate leukocytes. SCD is used within an extracorporeal blood circuit/CKRT

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certainty of evidence, one had a low certainty of evidence, and one had a moderate certainty of evidence. Polymyxin-B hemoperfusion and plasma exchange, two extracorporeal blood purification modalities, had very low and low certainty of evidence, respectively. See **Supplementary Table 8** (http://links.lww.com/CCM/H375) for detailed reasons for downgrading.

Secondary Outcomes: LOS in ICU and MV days

A total of 22 RCTs (consisting of 13 intervention arms and 1,568 participants) compared the effectiveness of reducing LOS in the ICU (**Supplementary Fig. 2**, http://links.lww.com/CCM/H375). Plasma exchange (MD: –7.00 d; 95% CI, –13.00 to –0.70 d), HA330 + high-volume CVVH (MD: –6.10 d; 95% CI, –9.88 to –2.32 d), HA330 (MD: –5.48 d; 95% CI, –8.12 to –2.84 d) and standard-volume CVVH (MD: –4.27 d; 95% CI, –6.86 to –1.69 d) were associated with shorter LOS in the ICU in comparison with standard care (**Fig. 3*A*; Supplementary Tables 9** and **10**, http://links.lww.com/CCM/H375). Low heterogeneity (I^2 = 34.9%; 95% CI, 0.0–68.0%) and no funnel plot asymmetry were detected (**Supplementary Fig. 3**, http://links.lww.com/CCM/H375). The certainty of evidence was rated as very low (**Supplementary Table 11**, http://links.lww.com/CCM/H375).

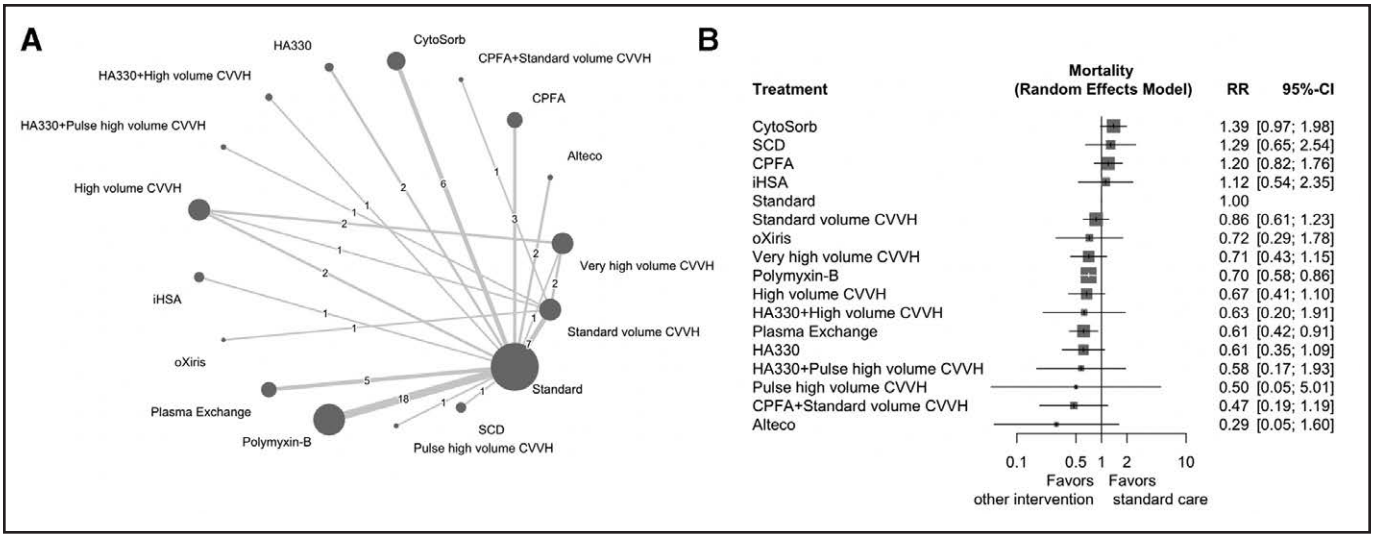

Figure 2. Network plot of eligible comparisons among interventions for mortality (**A**) and forest plot of eligible comparisons among interventions for mortality (**B**). The *network plot* depicts each intervention as a node, with *lines* indicating the direct comparison between different interventions. The size of the nodes and the width of the lines are weighted according to the number of participants within the intervention and the number of studies involved in the direct comparison, respectively. The *number written on each line* represents the number of studies involved in the direct comparison. CPFA = coupled plasma filtration and adsorption hemofiltration, CVVH = continuous venovenous hemofiltration, iHSA = immobilized human serum albumin, RR = relative risk, SCD = selective cytopheretic device.

Ten RCTs (consisting of 9 intervention arms and 712 participants) compared the effectiveness of reducing MV days (**Supplementary Fig. 4**, http://links.lww.com/CCM/H375). HA330+high-volume CVVH (MD: –6.50 d; 95% CI, –9.21 to –3.79 d), HA330 (MD: –4.40 d; 95% CI, –7.00 to –1.80 d) and standard-volume CVVH (MD: –2.91 d; 95% CI, –4.68 to –1.15 d) were beneficial in reducing MV days in comparison with standard care (**Fig. 3*B*; Supplementary Tables 12** and **13**, http://links.lww.com/CCM/H375). Low heterogeneity (I^2 = 38.9%; 95% CI, 0.0–81.0%) and no funnel plot asymmetry were detected (**Supplementary Fig. 5**, http://links.lww.com/CCM/H375). All three potential effective modalities were rated as having very low certainty of evidence (**Supplementary Table 14**, http://links.lww.com/CCM/H375).

Secondary Outcomes: AKI Occurrence Rate and Requirement of Kidney Replacement Therapy

Five RCTs (consisting of 3 intervention arms and 801 participants) compared the effectiveness of reducing AKI occurrence rate (**Supplementary Fig. 6**, http://links.lww.com/CCM/H375). No significant AKI risk reduction was observed with CytoSorb and polymyxin-B hemoperfusion. (**Fig. 4*A*; Supplementary Tables 15** and **16**, http://links.lww.com/CCM/H375) with low heterogeneity (I^2 = 0%; 95% CI, 0.0–84.7%) and no asymmetry in the funnel plot (**Supplementary Fig. 7**, http://links.lww.com/CCM/H375) The certainty of evidence was moderate to low (**Supplementary Table 17**, http://links.lww.com/CCM/H375).

Six RCTs comprising 490 participants compared the effectiveness of polymyxin-B hemoperfusion with standard care and depicted no reduction in requirement of kidney replacement therapy (RR: 0.75; 95% CI, 0.33–1.66) with high heterogeneity (I^2 = 73.0%; 95% CI, 33.0–88.0 %, p value < 0.01) and very low certainty of evidence (**Supplementary Table 18**, http://links.lww.com/CCM/H375; and **Fig. 4*B***).

Sensitivity Analysis

Some studies without clearly defined sepsis/septic shock were excluded from sensitivity analysis (20, 30, 31, 66–68). Finally, 52 RCTs (consisting of 16 intervention arms and 3,848 participants) that involved patients with sepsis or septic shock were included to compare the outcome of mortality (**Supplementary Fig. 8*A***, http://links.lww.com/CCM/H375). Polymyxin-B hemoperfusion and plasma exchange still showed survival benefits in comparison with standard care (**Supplementary Fig. 8*B***, http://links.lww.com/CCM/H375). Only polymyxin-B hemoperfusion was enrolled for renal-related outcome analysis (AKI and

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TABLE 2.
Findings in Network Meta-Analysis

Estimates of effects, CI, and certainty of the evidence for adult patients with severe infection or sepsis/septic shock by blood purification

Patients: adult patients with severe infection or sepsis/septic shock.

Interventions: 16 methodologies as below.

Comparator (reference): standard care.

Outcome: mortality.

Total studies Total participants	Relative Effect: RR (95% CI)	Anticipated Absolute Effect (95% CI)			Certainty of the Evidence
		Without Intervention	With Intervention	Difference	
Alteco	0.29 (0.05–1.20)	389 per 1,000	67 per 1,000	276 fewer per 1,000 (from 370 fewer to 234 more)	⊕○○○ Very low
CPFA	1.20 (0.82–1.76)	389 per 1,000	491 per 1,000	78 more per 1,000 (from 70 fewer to 296 more)	⊕○○○ Very low
CPFA + standard-volume CVVH	0.47 (0.19–1.19)	389 per 1,000	266 per 1,000	206 fewer per 1,000 (from 315 fewer to 74 more)	⊕○○○ Very low
Very high-volume CVVH	0.71 (0.43–1.15)	389 per 1,000	532 per 1,000	113 fewer per 1,000 (from 222 fewer to 58 more)	⊕○○○ Very low
Pulse high-volume CVVH	0.50 (0.05–5.01)	389 per 1,000	91 per 1,000	195 fewer per 1,000 (from 370 fewer to 1,000 more)	⊕○○○ Very low
High-volume CVVH	0.67 (0.41–1.10)	389 per 1,000	479 per 1,000	128 fewer per 1,000 (from 230 fewer to 39 more)	⊕○○○ Very low
Standard-volume CVVH	0.86 (0.61–1.23)	389 per 1,000	351 per 1,000	54 fewer per 1,000 (from 152 fewer to 90 more)	⊕○○○ Very low
CytoSorb	1.39 (0.97–1.98)	389 per 1,000	335 per 1,000	152 more per 1,000 (from 12 fewer to 381 more)	⊕⊕⊕○ Moderate
HA330	0.61 (0.35–1.09)	389 per 1,000	367 per 1,000	152 fewer per 1,000 (from 253 fewer to 35 more)	⊕○○○ Very low
HA330 + pulse high-volume CVVH	0.63 (0.20–1.91)	389 per 1,000	267 per 1,000	144 fewer per 1,000 (from 311 fewer to 354 more)	⊕○○○ Very low
HA330 + high-volume CVVH	0.58 (0.17–1.93)	389 per 1,000	167 per 1,000	163 fewer per 1,000 (from 323 fewer to 362 more)	⊕○○○ Very low
Immobilized human serum albumin	1.12 (0.54–2.35)	389 per 1,000	288 per 1,000	47 more per 1,000 (from 179 fewer to 525 more)	⊕○○○ Very low
oXiris	0.72 (0.29–1.78)	389 per 1,000	625 per 1,000	109 fewer per 1,000 (from 276 fewer to 304 more)	⊕○○○ Very low
Plasma exchange	0.61 (0.42–0.91)	389 per 1,000	265 per 1,000	152 fewer per 1,000 (from 226 fewer to 35 fewer)	⊕⊕○○ Low
Polymyxin-B	0.70 (0.58–0.86)	389 per 1,000	339 per 1,000	117 fewer per 1,000 (from 163 fewer to 54 fewer)	⊕○○○ Very low
Selective cytopheretic device	1.29 (0.65–1.54)	389 per 1,000	391 per 1,000	113 fewer per 1,000 (from 136 fewer to 210 more)	⊕○○○ Very low

CPFA = coupled plasma filtration and adsorption hemofiltration, CVVH = continuous venovenous hemofiltration, RR = relative risk.

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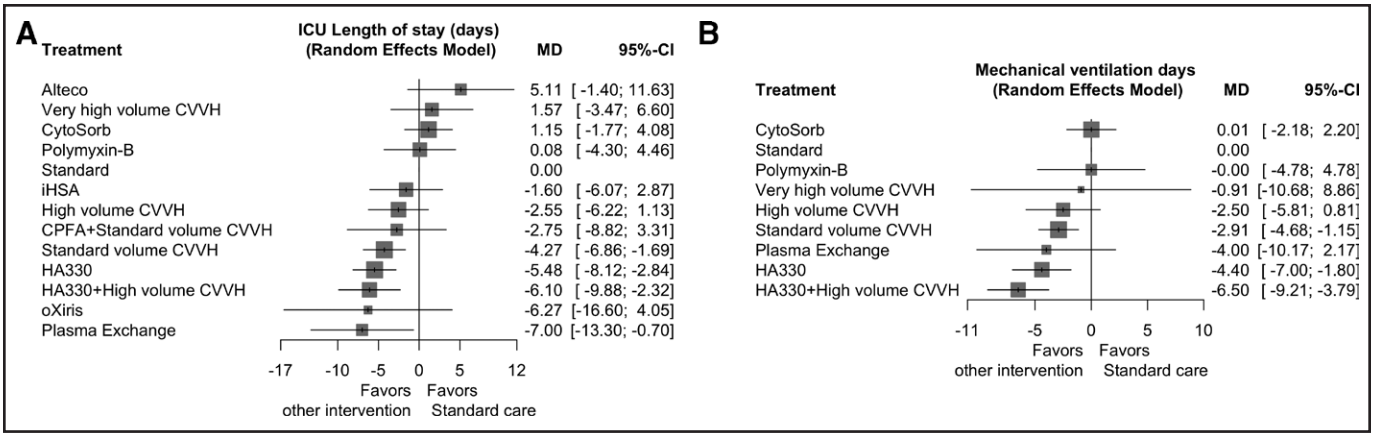

Figure 3. Forest plot of eligible comparisons among interventions for length of stay in ICU (**A**) and mechanical ventilation days (**B**). CPFA = coupled plasma filtration and adsorption hemofiltration, CVVH = continuous venovenous hemofiltration, iHSA = immobilized human serum albumin, MD = mean difference.

kidney replacement therapy) in this sensitivity analysis and polymyxin-B hemoperfusion was not associated with significantly lower AKI or kidney replacement therapy risk (**Supplementary Fig. 9, *A*** and ***B***, http://links.lww.com/CCM/H375). In this sensitivity analysis, three modalities (HA330+high-volume CVVH, HA330, and standard-volume CVVH) depicted significantly reduced LOS in the ICU (**Supplementary Fig. 9*C***, http://links.lww.com/CCM/H375) and reduced MV days (**Supplementary Fig. 9*D***, http://links.lww.com/CCM/H375).

We excluded studies published before 2013 and analyzed 33 studies with 3,067 participants and 15 interventions. HA330 hemoperfusion and plasma exchange was linked to lower mortality risk (**Supplementary Fig. 10, *A*** and ***B***, http://links.lww.com/CCM/H375).

Subgroup Analysis of Network Meta-Analysis

Subgroup analysis showed that plasma exchange was associated with lower mortality risk in low mortality subgroup (<70%) (**Supplementary Fig. 11, *A*** and ***B***, http://links.lww.com/CCM/H375), whereas polymyxin-B hemoperfusion was linked to decrease mortality risk in high mortality subgroup (≥70%) (**Supplementary Fig. 12, *A*** and ***B***, and **Supplementary Document 3**, http://links.lww.com/CCM/H375, **for detailed results**).

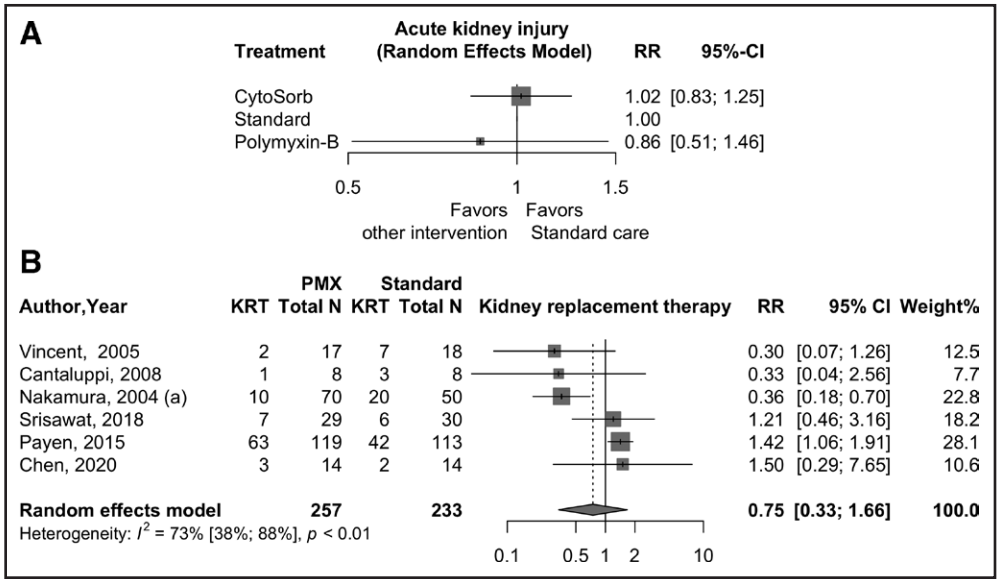

Figure 4. Forest plot of eligible comparisons among interventions for acute kidney injury occurrence rates (**A**) and requirement of kidney replacement therapy (KRT) (**B**). PMX = polymyxin B hemoperfusion, RR = relative risk.

Trial Sequential Analysis, Subgroup Analysis, and Sensitivity Analysis Regarding Polymyxin-B Hemoperfusion and Plasma Exchange

To assess whether the benefit of polymyxin-B hemoperfusion is premature, we conducted trial sequential analysis (TSA). TSA demonstrated a true-positive result with nearly sufficient sample size (**Supplementary Fig. 13** and **Supplementary Document 4**, http://links.lww.com/CCM/H375).

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To further examine the robustness of the effectiveness of polymyxin-B hemoperfusion, we conducted pairwise meta-analysis with subgroup analysis. The studies were divided into different groups based on population (Asia vs Europe/USA) and sepsis guideline publication year (before 2013, 2013–2017, and after 2017) (77, 78). Sensitivity analysis was performed by excluding studies with a high RoB (**Supplementary Fig. 14,** ***A*** and ***B***, http://links.lww.com/CCM/H375). The subgroup analysis revealed the intervention was more effective in the Asia population and older studies. However, after excluding studies with a high RoB, the sensitivity analysis did not show a survival benefit.

TSA analysis also showed true positive results for mortality with plasma exchange, but additional studies are needed to confirm its benefits due to the insufficient sample size (**Supplementary Fig. 15** and **Supplementary Document 4**, http://links.lww.com/CCM/H375).

Assessing Risk-of-Bias (RoB)

The overall RoB assessment of the enrolled RCTs is summarized in **Supplementary Fig. 16,** ***A*** and ***B*** (http://links.lww.com/CCM/H375). Most (38/60) of the bias in the included RCTs resulted from randomization without concealment. Therefore, the RoB in this domain was assessed as "some concern." The RoB in the domain of selection of the reported results was also judged as "some concern" in some studies (18/60) due to no registration of the trials. In the domain of bias due to missing outcome data, one RCT (18) had high RoB because more than 20% of patients were lost to follow-up. For the overall RoB, 25% (15/60) of enrolled RCTs had a high RoB, 43.3% (26/60) had "some concern" RoB and 31.7% (19/60) had low RoB.

DISCUSSION

In this NMA, three points are worth summarizing. First, polymyxin-B hemoperfusion and plasma exchange may have potential survival benefits compared with standard care. Second, the use of plasma exchange and HA330 hemoperfusion, with or without CVVH, may lead to a reduction in ICU days or MV days. Third, we observed high heterogeneity in the mortality rates among the enrolled studies, which warrants further discussion.

Our study found that polymyxin-B hemoperfusion may reduce mortality. However, weak recommendation against its use in the Surviving Sepsis Campaign Guideline 2021 (2) was based on the following reasons: 1) results not being robust in sensitivity analysis, 2) low quality of evidence, and 3) concerns about cost-effectiveness and potential adverse effects. Our updated meta-analysis on polymyxin-B hemoperfusion included 18 trials, 5 of which were not included in previous meta-analyses (14, 27, 45, 46, 52). For confirming the effectiveness of polymyxin-B hemoperfusion, we additionally conducted TSA. If the cumulative Z curve endpoint falls within the O'Brien-Fleming monitoring boundary but outside the conventional test, it may lead to premature conclusions with conventional meta-analysis and inconclusive results with TSA. Furthermore, crossing the required information size line or monitoring boundary allows for more confident conclusions (79, 80). In our study, the end of the cumulative *Z* curve crossed the O'Brien-Fleming monitoring boundaries and was close to the line of required information size, indicating a true-positive result with nearly sufficient sample size (Supplementary Fig. 14, http://links.lww.com/CCM/H375). However, significant treatment effect heterogeneity of polymyxin-B hemoperfusion was observed between groups (Supplementary Figs. 11*B* and 13, http://links.lww.com/CCM/H375), and sensitivity analysis raised concerns about the result's robustness, consistent with a previous systematic review (10). Our scatter plot showed high mortality rates in the standard care group for early trials examining polymyxin-B hemoperfusion's effectiveness (**Supplementary Fig. 17**, http://links.lww.com/CCM/H375). In brief, the interpretation of the pooled estimated effect of polymyxin-B hemoperfusion should be approached with caution due to the presence of heterogeneity in treatment response.

Our analysis showed that plasma exchange may have benefits for adult septic patients, which is not clearly stated in the Surviving Sepsis Campaign guideline 2021 (2). We included three recent studies that were not included in a previous systematic review (31, 63, 72). TSA showed a true-positive result from plasma exchange in terms of mortality (Supplementary Fig. 15, http://links.lww.com/CCM/H375). Notably, two studies examined the effectiveness of plasma exchange in sepsis with specific complications: Faqihi et al (31) enrolled critically ill COVID-19 patients with acute respiratory distress syndrome or sepsis/septic shock, whereas Weng et al (72) enrolled septic patients with diffuse intravascular

coagulation. Future RCTs are needed to determine the most beneficial application of plasma exchange for adult septic patients with different associated conditions.

Our study has multiple strengths. First, we conducted an NMA to evaluate the treatment effects of 16 extracorporeal blood purification modalities, including novel extracorporeal blood purification modalities that were not previously discussed. Second, we updated the comprehensive systematic review by including newly published articles. Third, we examined critical illness-related secondary outcome which was not discussed. Fourth, we regrouped CVVH treatment into four different doses to analyze the treatment benefit of different doses. By contrast, the present study had some limitations. First, most of the extracorporeal blood purification modalities only had a direct comparison with standard care; therefore, the comparison between different modalities from NMA was largely based on indirect evidence. Second, our studies covered a period from 1999 to 2022, and the mortality rates varied among them. As previously noted, the transitivity assumption in NMA may present a challenge in our analysis. Third, the limited number of RCTs with few cases resulted in statistically nonsignificant differences with wide intervals between the intervention and control groups in many extracorporeal blood purification modalities. In our study, we ranked the interventions using P-scores instead of surface under the cumulative ranking values (81), and the additional TSA analysis was not part of our initial PROSPERO protocol.

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Conclusions

This updated NMA suggests that polymyxin-B hemoperfusion and plasma exchange may improve survival in adult patients with severe infection or sepsis/septic shock in addition to standard care. However, a clear recommendation is difficult to provide based on these limited references and the uncertainty of evidence. Further studies are needed to identify participants who may benefit from extracorporeal blood purification and define the adequate dose and treatment protocol due to high heterogeneity in treatment response.

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The dataset supporting the conclusions of this article is included within the article and its additional files.

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