

ORIGINAL RESEARCH

Hemodynamic Effects of Therapeutic Plasma Exchange and High-Volume Hemofiltration in Refractory Septic Shock: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF) are adjuncts to facilitate down-titration. This meta-analysis compared TPE, HVHF, and standard of care (SOC) on NE dose and clinical outcomes.

Methods : Analysis was performed using Review Manager software, and random- and fixed-effects models were used to calculate pooled estimates for the data.

Results : Both TPE and HVHF were associated with reductions in NE requirements in the overall analysis (TPE: MD -0.21 , 95% CI -0.27 to -0.14 , $p < 0.00001$; HVHF: MD -0.50 , 95% CI -0.71 to -0.30 , $p < 0.00001$), with a significant indirect subgroup difference ($p = 0.006$). Within 6 hours, the pooled NE reduction was significant (SMD -1.06 , 95% CI -1.97 to -0.15 ; $p = 0.02$); TPE showed a significant reduction (SMD -1.91 , 95% CI -2.67 to -1.15 ; $p < 0.00001$), whereas HVHF did not reach statistical significance (SMD -0.60 , 95% CI -1.24 to 0.03 ; $p = 0.06$). No significant overall reduction was observed at 12 hours, whereas a significant pooled reduction was observed at 24 hours (SMD -1.54 , 95% CI -3.02 to -0.07 ; $p = 0.04$); the HVHF estimate at 24 hours was derived from a single study. TPE significantly reduced stroke volume variation (SMD -0.90 , 95% CI -1.29 to -0.51 ; $p < 0.00001$) and improved $\text{PaO}_2/\text{FiO}_2$ (SMD 2.41 , 95% CI 0.22 – 4.61 ; $p = 0.03$). ICU-free, vasopressor-free, and RRT-free days were not significantly improved, whereas TPE was associated with lower 28-day mortality (RR 0.60 , 95% CI 0.47 – 0.77 ; $p < 0.0001$).

Conclusion : Both TPE and HVHF were associated with reductions in vasopressor requirements, with different temporal patterns observed across indirect subgroup analyses. TPE was also associated with lower 28-day mortality; however, direct comparative evidence between the two modalities remains limited.

Keywords: Critical care; Norepinephrine; Refractory septic shock; Therapeutic plasma exchange; Vasopressor sparing



INTRODUCTION

Septic shock is defined according to the Sepsis-3 criteria as persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg and a serum lactate level > 2 mmol/L despite adequate volume resuscitation. Refractory septic shock represents a more severe form of circulatory failure characterized by persistent hypotension and vasopressor dependency despite adequate resuscitation. However, no universally accepted definition nor norepinephrine threshold has been established for refractory septic shock, with thresholds reported across studies ranging from approximately 0.2 to 4.0 $\mu\text{g/kg/min}$. This variability complicates both clinical decision-making and the standardization of research populations. Patients with refractory septic shock commonly exhibit profound vasoplegia, endothelial dysfunction, and dysregulated immune responses, contributing to persistent tissue hypoperfusion, organ dysfunction, and high mortality.¹⁻⁴

The ultimate consequence of prolonged shock is cellular hypoxia and persistent inflammation, which drive ongoing vasodilation, impair myocardial

performance, and disrupt microcirculatory flow and tissue perfusion, regardless of the initial trigger. At this stage, shock becomes unresponsive to catecholamines because conventional treatment with fluids and vasopressors is insufficient to counteract a complex, self-perpetuating pathophysiological process. Catecholamine-refractory shock is therefore marked by vascular hyporesponsiveness, in which blood vessels fail to constrict adequately despite elevated levels of endogenous or administered catecholamines. This refractory vasoplegia arises from multiple interrelated mechanism.³

Norepinephrine remains the first-line vasopressor in septic shock due to its potent α -adrenergic vasoconstrictive effects and relatively favorable safety profile compared with other agents. The required NE dose is widely regarded as a surrogate marker of vasoplegia severity and overall vasopressor dependency. Higher NE requirements are associated with worse clinical outcomes, including increased mortality. Therefore, strategies that can reduce or “spare” vasopressor use while achieving early hemodynamic stabilization have become an important focus of critical care research. Achieving rapid stabilization not only improves organ perfusion but may

also limit the adverse effects associated with prolonged high-dose vasopressor exposure.^{5,6}

In recent years, extracorporeal blood purification techniques such as therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF) have emerged as potential adjunctive therapies in refractory septic shock. TPE involves the removal and replacement of plasma to eliminate circulating inflammatory mediators, endotoxins, and harmful cytokines that contribute to vasoplegia and organ dysfunction.⁷ HVHF, on the other hand, utilizes high ultrafiltration rates to enhance the clearance of pro-inflammatory substances while simultaneously supporting renal function and fluid balance.⁸ Both techniques aim to modulate the dysregulated immune response and restore hemodynamic stability, thereby reducing dependence on vasopressors.^{7,8}

Despite growing clinical interest, the comparative effectiveness of TPE and HVHF in refractory septic shock remains unclear. Some studies suggest that TPE may provide more rapid hemodynamic improvement through targeted removal of vasoactive mediators, whereas others indicate that HVHF may be more beneficial due to continuous cytokine

clearance and better metabolic control. Additionally, evidence regarding their impact on clinical outcomes such as mortality, length of intensive care stay, and organ recovery remains inconsistent. Most previous studies have been small, heterogeneous, and observational in nature, limiting the generalizability of their findings.^{9,10}

Given these uncertainties, this study aims to systematically evaluate and compare the effects of TPE, HVHF, and standard of care (SOC) on norepinephrine dose reduction and key clinical outcomes in patients with refractory septic shock. By synthesizing available evidence through meta-analysis, this study seeks to explore differences in hemodynamic response patterns between modalities in achieving early hemodynamic stabilization, reducing vasopressor dependency, and ultimately improving patient survival.

METHODS

Study Selection Criteria

This systematic review employed a PICO framework to identify and synthesize evidence on the hemodynamic effects and clinical outcome of extracorporeal blood purification modalities in septic shock. Population included adult patients (≥ 18 years) diagnosed with septic shock according to Sepsis-2 or Sepsis-3 criteria,

as defined in the original studies. Patients were required to be admitted to intensive care units and to require vasopressor support at baseline.

The interventions of interest were:

1. Therapeutic Plasma Exchange (TPE), and
2. High-Volume Hemofiltration (HVHF), administered as adjunctive therapies to standard sepsis management.

Given the limited availability of direct head-to-head randomized trials, two analytical approaches were adopted:

1. comparison of TPE versus standard of care (SOC) for clinical outcomes, and
2. pre-post within-group analyses of hemodynamic parameters for both TPE and HVHF, followed by indirect subgroup comparisons between modalities.

The primary outcome was the change in norepinephrine (NE) dose over time, expressed as a vasopressor-sparing effect. Secondary outcomes included clinical outcome and changes in mean arterial pressure (MAP), MAP/NE ratio, lactate, PaO₂/FiO₂, cardiac index, systemic vascular resistance index, and fluid balance, when available.

Database Searching and Systematic

Literature Screening

We included randomized controlled trials, prospective cohort studies, and retrospective observational studies that:

1. Enrolled adult patients with septic shock,
2. Reported the use of TPE or HVHF as an intervention,
3. Provided quantitative hemodynamic data before and after intervention (e.g., NE dose, MAP) and clinical outcome,
4. Reported sufficient statistical information (mean, SD, or convertible median and IQR) to allow effect size calculation.

We excluded case reports, small case series (<5 patients), narrative reviews, editorials, conference abstracts without full data, animal studies, and in vitro studies.

A comprehensive search of PubMed, ScienceDirect, Google Scholar, and EBSCO was performed for literature published from 2001 until 2025. The search strategy combined controlled vocabulary and free-text terms including:

“septic shock” “therapeutic plasma exchange,” “plasmapheresis,” “high-volume hemofiltration,” “hemoperfusion,” “norepinephrine,” “vasopressor,” “hemodynamics,” and “blood purification.”

Two independent reviewers screened titles and abstracts for relevance. Full texts of potentially eligible articles were retrieved and assessed for inclusion. Disagreements were resolved by consensus. Duplicate records were removed prior to screening.

Statistical Analysis

Meta-analysis was performed using Review Manager. Continuous outcomes were summarized using mean differences (MDs) when the same measurement scale was used across studies and standardized mean differences (SMDs) when outcomes were reported using different scales or measurement approaches. Dichotomous outcomes were summarized using risk ratios (RRs), with corresponding 95% confidence intervals (CIs). For pre-post analyses, change from baseline was calculated as the post-intervention value minus the baseline value. When the standard deviation of the change was not reported, it was estimated using a within-participant correlation coefficient of 0.5. Statistical heterogeneity was assessed using the I^2 statistic. Random-effects models were applied when substantial clinical or statistical heterogeneity was present, whereas fixed-effect models were used when heterogeneity was limited. Subgroup analyses were conducted to

explore differences between TPE and HVHF; because these comparisons were indirect rather than based on head-to-head randomized trials, subgroup differences were interpreted cautiously. A two-sided p value <0.05 was considered statistically significant.

Data Extraction

Patients Characteristics

Across included studies, all participants were adults with septic shock requiring vasopressor support. Study populations varied in terms of age distribution, baseline severity scores, comorbidities, and sources of infection.

Baseline characteristics extracted included:

- Sample size,
- Mean age,
- Sex distribution,
- Baseline NE dose,
- Baseline MAP,
- Severity scores (e.g., SOFA, APACHE II), when available.

Outcome

The primary outcome was the change in norepinephrine dose from baseline at predefined time points (6 h, 12 h, and 24 h). Secondary hemodynamic outcomes included:

- Change in MAP,
- MAP/NE ratio,
- Lactate,

- PaO₂/FiO₂,
- Cardiac index,
- Systemic vascular resistance index (SVRI),
- Fluid balance.
- Clinical outcome.

When outcomes were reported as medians and interquartile ranges, mean and standard deviation were estimated using established conversion methods (Wan et al.).

Definition of Outcome Measurement

- Norepinephrine dose was expressed in µg/kg/min or equivalent units, as reported.
- Early hemodynamic response was defined as changes observed within 6 hours.
- Sustained vasopressor sparing was defined as changes observed at 24 hours.
- Change from baseline was calculated as:

$$\Delta = \text{Post-intervention value} - \text{Baseline value.}$$

For studies that did not report the SD of change, it was estimated using a correlation coefficient ($r = 0.5$), according to standard meta-analytic methods.

Risk Of Bias And Study Quality

Risk of bias was assessed according to study design. Randomized controlled

trials (RCTs) were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, which assesses bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Non-randomized and observational studies were evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, which assesses bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported results. Risk-of-bias judgments were reported for each domain and summarized for each included study.

Certainty of Evidence

The certainty of evidence for the prespecified outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Certainty was evaluated across five domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations, and was classified as high, moderate, low, or very low. Outcomes were also categorized according to their clinical importance as critical or important. The GRADE assessment was

summarized in a Summary of Findings table.

RESULT

According to the standard PRISMA protocol as the foundation of this study, our initial search yielded 257 articles. After removing 120 duplicated entries, 137 articles remained for title and abstract

screening. From this screening process, 119 articles were excluded for not meeting the required criteria. Eighteen reports were sought for retrieval; two could not be retrieved. Sixteen full-text reports were assessed for eligibility, of which six were excluded, resulting in 10 included studies.

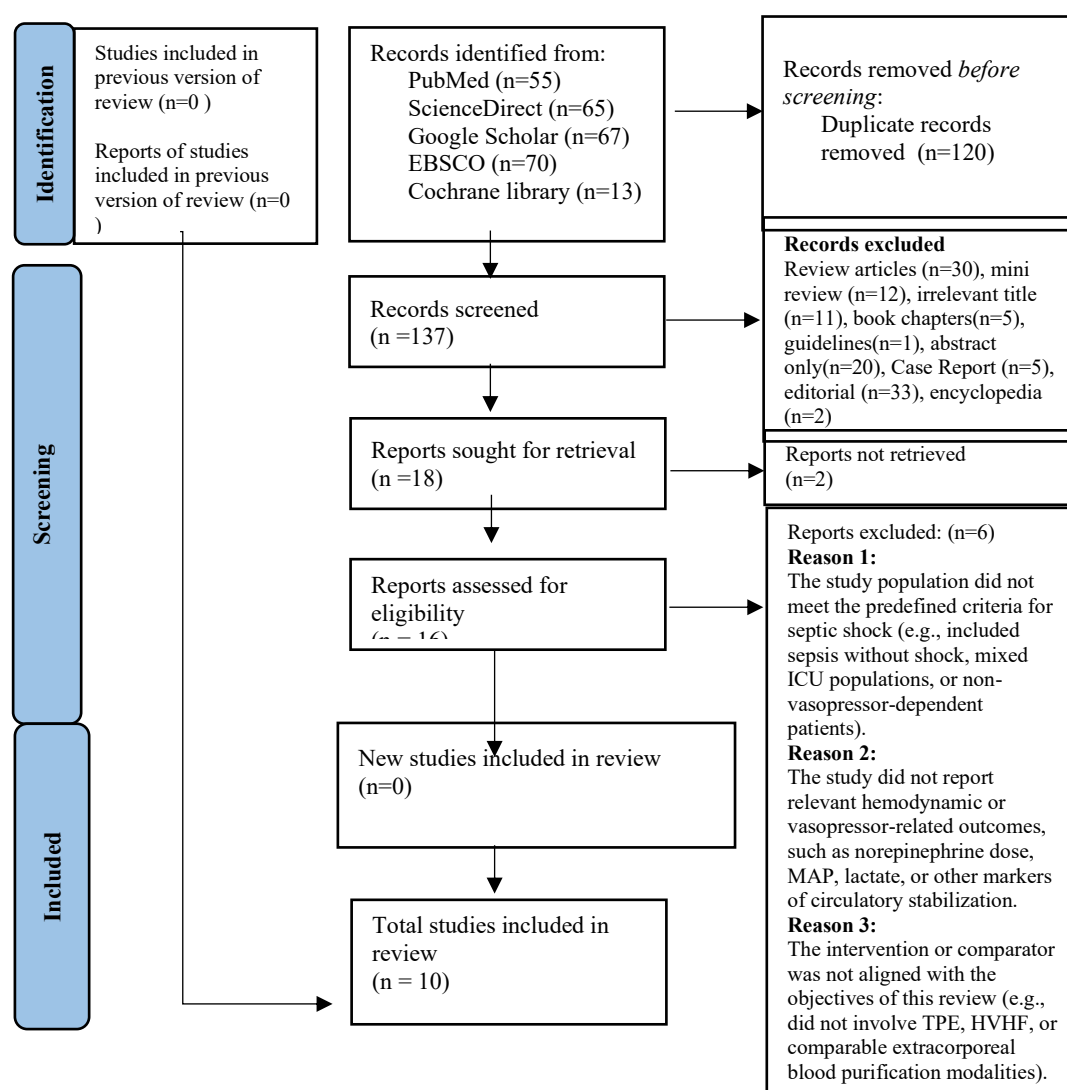


Figure 1. PRISMA 2020 flow diagram used to identify the analyzed study in this review.

Following our last screening method, we found ten studies that met the inclusion criteria, aligning with our PICO criteria, and were published within the last 25 years. Moreover,

all of the included studies were available in full-text format. No additional inclusion studies were obtained from the previous review studies. We also manually screened the

reference lists of previous systematic reviews and meta-analyses related to our objective to secure all potentially eligible literature; no additional studies were found to be included as “studies from other sources or review sources.”

Risk Of Bias From Included Studies

Risk of bias was assessed according to study design, and the results are presented in Figure 2 and 3. The assessment was independently performed by two reviewers, and disagreements were resolved through discussion and

consensus. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, whereas non-randomized and observational studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Domain-specific judgments were made for each study, followed by an overall risk-of-bias assessment. The detailed risk-of-bias judgments for all included studies are summarized in Figure 2 and 3.

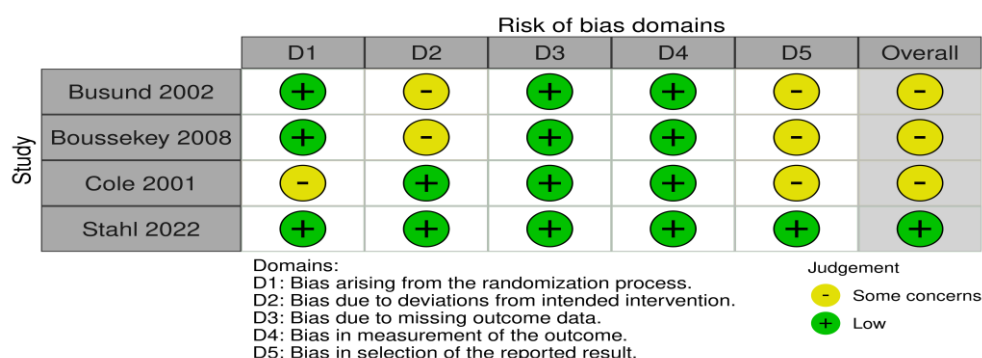


Figure 2. Risk-of-bias assessment of randomized controlled trials using RoB 2

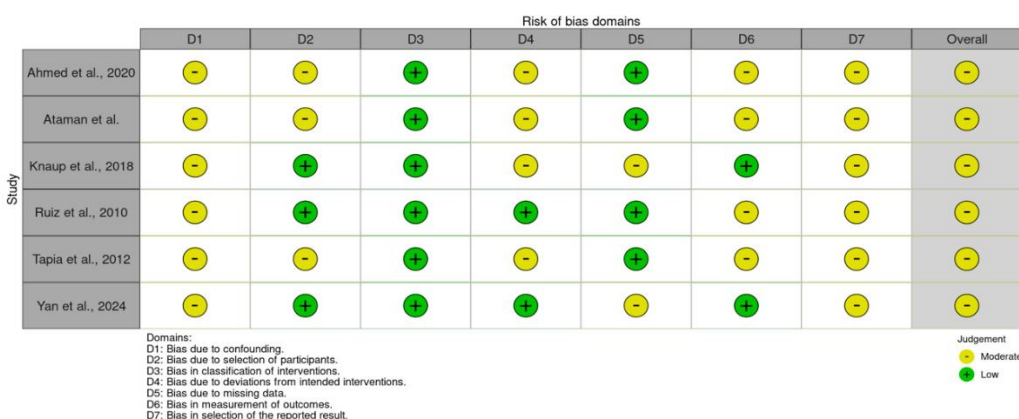


Figure 3. Risk-of-bias assessment of non-randomized and observational studies using ROBINS-I

CHARACTERISTICS OF THE STUDY INCLUDED

Table 1. Characteristics of the studies.

Authors, Year	Study Design	Country	Patients' Criteria of Eligibility	Outcome
Ahmed et al., 2020 ¹¹	Prospective observational study	Egypt	Adult patients with severe septic shock with onset <12 hours, requiring high-dose norepinephrine (>0.6 µg/kg/min), admitted to ICU. All patients received standard sepsis management plus TPE within 4 hours of ICU admission	Improved hemodynamic stability, reduced norepinephrine requirement, enhanced vasopressor efficiency, improved fluid balance, increased vascular tone and cardiac performance, more stable preload status, and reduced inflammatory activity.
Ataman et al., 2002 ¹²	Retrospective observational study	Germany	Adult patients with norepinephrine-refractory septic shock, defined by persistent hypotension despite adequate volume resuscitation requiring continuous intravenous norepinephrine to maintain MAP.	No significant hemodynamic or metabolic improvement within 24 h after plasmapheresis; mortality remained high, suggesting no short-term benefit as rescue therapy in norepinephrine-refractory septic shock.
Boussekey et al., 2008 ¹³	Prospective randomized controlled trial	France	Adult patients with septic shock and acute renal failure (ARF) requiring renal replacement therapy (criteria: urine output <200 mL/12 h or anuria >12 h, serum urea >30 mmol/L, serum creatinine >500 µmol/L, or doubling of baseline creatinine). Excluded were patients with obstructive or prerenal renal failure, severe chronic kidney disease (CrCl <30 mL/min), severe immunosuppression, moribund state, delayed septic shock/ARF (>5 days after ICU admission), or early death after randomization.	High-volume hemofiltration (HVHF) resulted in a more rapid reduction in norepinephrine requirements at 24 hours compared with low-volume hemofiltration in septic shock patients with acute renal failure. HVHF showed a trend toward increased urine output, but no significant differences were observed in lactate levels, PaO ₂ /FiO ₂ ratio, organ dysfunction scores, duration of mechanical ventilation, renal replacement therapy, ICU length of stay, or 28-day mortality
Cole et al., 2001 ¹⁴	Randomized controlled trial	France	Adult patients with septic shock and multi-organ failure, requiring norepinephrine to maintain MAP ≥70 mmHg, with acute	High-volume hemofiltration (HVHF) produced a greater and more rapid reduction in norepinephrine

			renal failure requiring renal replacement therapy. All patients were mechanically ventilated and managed in a tertiary ICU.	requirements compared with standard continuous venovenous hemofiltration (CVVH). HVHF significantly reduced circulating inflammatory mediators (C3a, C5a), whereas no sustained improvement in other hemodynamic variables or clinical outcomes was demonstrated.
Knaup et al., 2018 ⁹	Prospective observational study	Germany	Adult patients with early septic shock (onset < 12 h) requiring high-dose norepinephrine (> 0.4 µg/kg/min) despite adequate fluid resuscitation (≥ 30 mL/kg crystalloids), treated according to SSC guidelines. TPE initiated within 6 h after inclusion. Excluded were pregnancy/breastfeeding, age <18 years, and end-stage chronic disease.	Early TPE was feasible and safe, with no procedure-related adverse events, and was associated with a rapid reduction in norepinephrine requirements while maintaining MAP ≥65 mmHg. TPE significantly reduced proinflammatory cytokines and endothelial permeability mediators and restored endothelial barrier function ex vivo. 28-day mortality remained high, and a survival benefit could not be established, indicating the need for adequately powered randomized trials.
Ruiz et al., 2010 ¹⁵	Prospective non-randomized observational study	Belgium	Adult patients with severe hyperdynamic septic shock, requiring norepinephrine ≥0.3 µg/kg/min to maintain MAP ≥65 mmHg for ≥1 h, cardiac index ≥3.0 L/min/m ² , and progressive hyperlactatemia despite full resuscitation. All patients were mechanically ventilated and had pulmonary artery catheters. Excluded were patients without full resuscitation commitment, active bleeding, or undrained surgical sepsis.	HVHF improved sublingual microcirculatory flow, with increased microcirculatory flow index and proportion of perfused microvessels persisting after treatment, without deterioration of microvascular density or heterogeneity, despite increased systemic vascular resistance. Mean arterial pressure increased and lactate levels decreased, indicating hemodynamic and microcirculatory improvement without microcirculatory compromise.
Stahl et al., 2022 ¹⁶	Randomized controlled trial	Germany	Adult patients with septic shock (SEPSIS-3) with vasopressor onset < 24 h and high-dose norepinephrine	Adjunctive TPE resulted in a significantly greater and continuous reduction in norepinephrine dose and

			requirement (≥ 0.4 $\mu\text{g/kg/min}$) despite adequate fluid resuscitation (≥ 30 mL/kg crystalloids). TPE performed within 6 h after randomization. Excluded were pregnancy/breastfeeding, age <18 years, end-stage chronic disease, or limitation of life-sustaining therapy.	serum lactate over the first 24 h compared with SOC alone. TPE was associated with removal of proinflammatory and endothelial injury mediators. Higher baseline lactate predicted greater hemodynamic response to TPE, suggesting a potential predictor of treatment efficacy, while effects on hard clinical outcomes require further evaluation. A single 6-hour session of HVHF significantly reduced norepinephrine requirements by the 4th hour, with concurrent improvement in hemodynamic, metabolic, respiratory, and organ function parameters, sustained through 6 h. Responders showed markedly lower hospital mortality compared with non-responders and with SOFA-predicted mortality, indicating an early hemodynamic and organ function benefit of short-term HVHF in refractory septic shock. Plasmapheresis was associated with significantly reduced mortality, including 28-day mortality (HR 0.50; 95% CI 0.27–0.94), in-hospital mortality (HR 0.38; 95% CI 0.20–0.71), and 1-year mortality (HR 0.44; 95% CI 0.26–0.74). PE was also associated with improvement in organ function and hemodynamics, with decreasing SOFA scores, norepinephrine dose, coagulation and inflammatory markers, and increases in hematologic indices over time compared with conventional therapy. Plasmapheresis was
Tapia et al., 2012 ¹⁷	Prospective cohort study	Brazil	Adult patients with refractory severe septic shock, defined as norepinephrine ≥ 0.3 $\mu\text{g/kg/min}$ to maintain MAP 70–80 mmHg and progressive lactic acidosis, refractory for ≥ 6 h to Surviving Sepsis Campaign–recommended therapy. All patients had full commitment to resuscitation; HVHF was initiated irrespective of renal function. Excluded were patients with limitation of therapy or those who responded to standard resuscitation within the first 6 h.	
Yan et al., 2024 ¹⁸	Retrospective cohort study	United States	Adult ICU patients meeting Sepsis-3 criteria with multiple organ failure (MOF) identified from the MIMIC-IV database. Excluded were repeated ICU admissions, ICU stay <48 h, pregnancy/lactation, end-stage heart failure or end-stage renal disease, and sepsis developing after ICU admission. Patients receiving plasmapheresis (PE) during ICU stay were matched to those receiving conventional therapy.	
Busund et	Randomized	Russia	Consecutive patients with	

al., 2002 ¹⁹	controlled trial	severe sepsis or septic shock admitted to the ICU; 106 patients were randomized to standard therapy or standard therapy plus plasmapheresis.	associated with lower 28-day all-cause mortality compared with standard therapy (33.3% vs 53.8%; RR 0.61). Treatment-related adverse events were generally transient, including hypotension and one allergic reaction to fresh frozen plasma.
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Time-Dependent Effects On Norepinephrine Dose

Time-Dependent Effects on Norepinephrine Dose Within 6 Hours (0–6 h).

As shown in Figure 4, the pooled analysis demonstrated a significant reduction in norepinephrine dose within 6 hours after extracorporeal therapy (SMD -1.06 ; 95% CI -1.97 to -0.15 ; $p = 0.02$), with substantial heterogeneity ($I^2 = 70\%$). TPE was associated with a significant reduction in norepinephrine dose (SMD -1.91 ; 95% CI -2.67 to -1.15 ; $p < 0.00001$), whereas the pooled effect for HVHF did not reach statistical significance (SMD -0.60 ; 95% CI -1.24 to 0.03 ; $p = 0.06$; $I^2 = 0\%$). The test for subgroup differences was significant ($p = 0.01$), suggesting different effect estimates between the two modalities; however, this finding represents an indirect subgroup comparison and should not be interpreted as evidence of superiority.

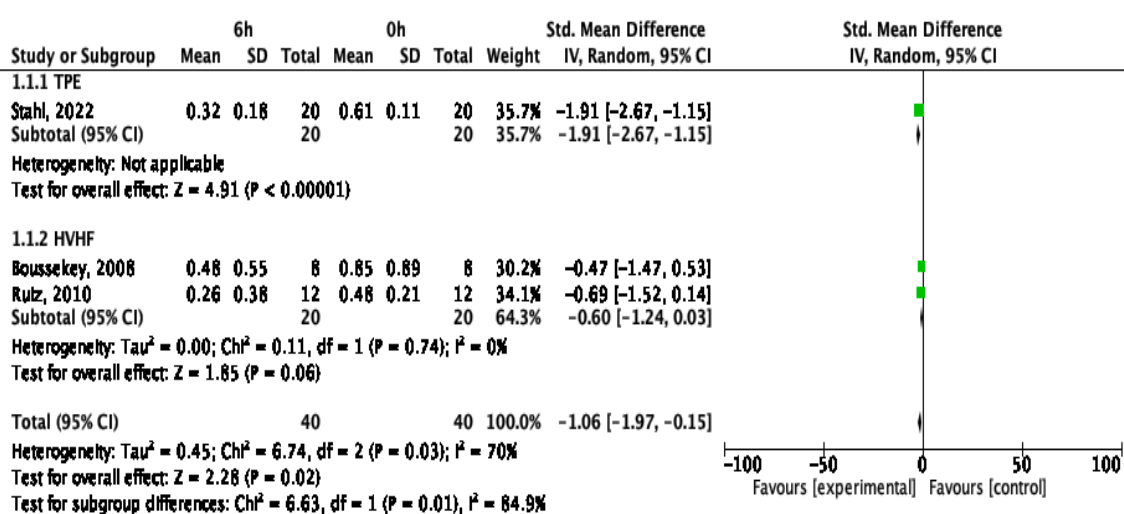


Figure 4. Forest plot of norepinephrine dose reduction within 6 hours (0–6 h) following therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF).

Within 12 Hours (0–12 h)

As shown in figure 5, neither TPE nor HVHF showed a significant reduction in norepinephrine dose at 12 hours compared with baseline (overall SMD -0.33 ; 95% CI

-0.87 to 0.21 ; $p = 0.23$). No heterogeneity was detected ($I^2 = 0\%$), and no significant differences were observed between subgroups.

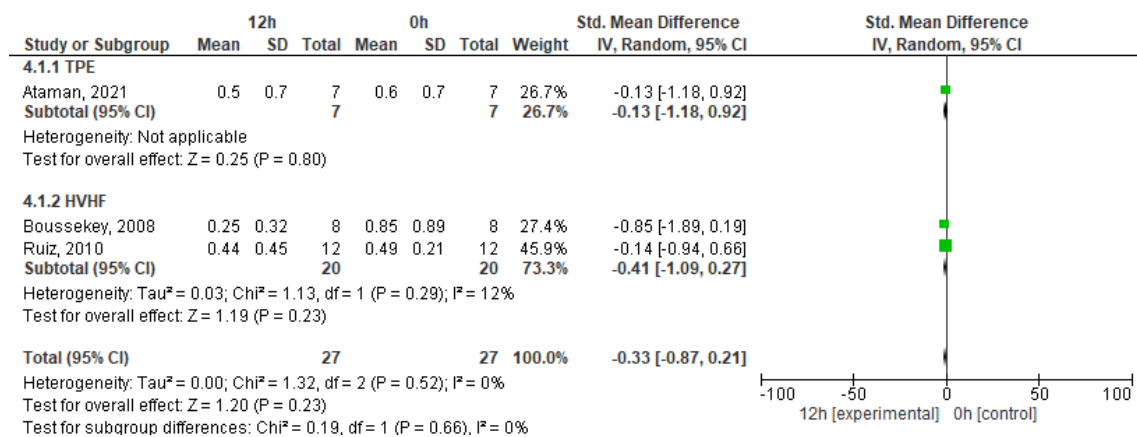


Figure 5. Forest plot of norepinephrine dose reduction within 12 hours (0–12 h) following therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF).

Within 24 Hours (0–24 h)

As shown in figure 6, a significant reduction in norepinephrine dose was observed at 24 hours (SMD -1.54 ; 95% CI -3.02 to -0.07 ; $p = 0.04$), although heterogeneity was substantial ($I^2 = 83\%$). Subgroup analysis revealed that TPE did

not achieve a statistically significant effect (SMD -1.35 ; 95% CI -3.67 to 0.97 ; $p = 0.25$; $I^2 = 92\%$), whereas HVHF demonstrated a significant reduction based on a single study (SMD -1.93 ; $p = 0.002$).

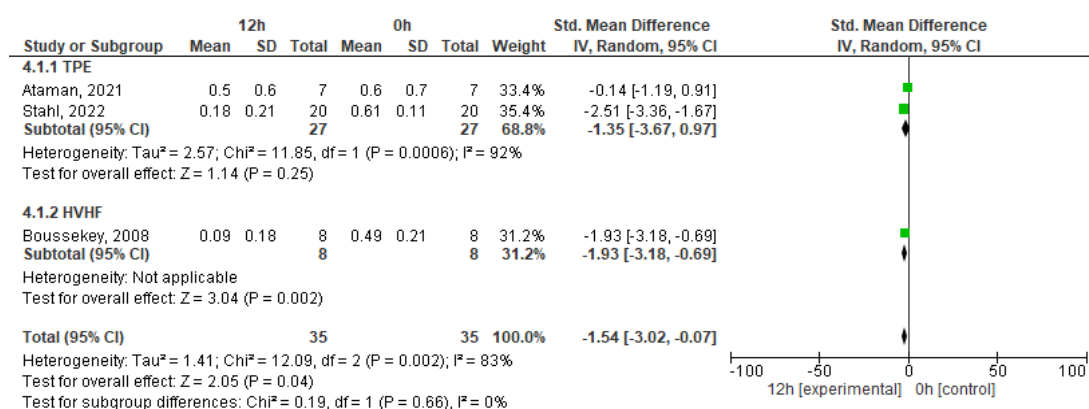


Figure 6. Forest plot of norepinephrine dose reduction within 24 hours (0–24 h) following therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF).

Therapeutic Plasma Exchange (TPE) Alone Hemodynamic Parameters

Mean Arterial Pressure to Norepinephrine
Ratio (MAP/NE)

As shown in figure 7, TPE alone did not result in a significant improvement in the MAP/norepinephrine ratio compared with control (SMD -0.01 ; 95% CI -0.99 to

0.97 ; $p = 0.98$), indicating no meaningful enhancement in hemodynamic efficiency. Substantial heterogeneity was observed among studies ($I^2 = 77\%$), likely reflecting differences in indications, timing of TPE initiation, treatment protocols, and baseline disease severity.

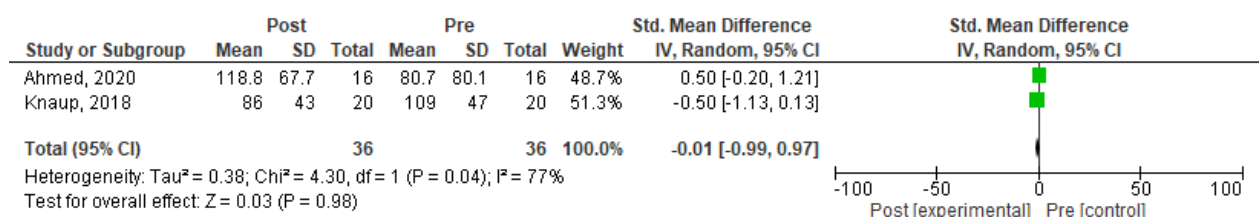


Figure 7. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on the mean arterial pressure to norepinephrine ratio (MAP/NE).

Systemic Vascular Resistance Index (SVRI) as shown in figure 8, no significant change in SVRI was observed with TPE compared with control (SMD -0.13 ; 95% CI -0.85 to 0.58 ; $p = 0.72$). Considerable

heterogeneity was present ($I^2 = 72\%$), suggesting variability across studies. Overall, these findings indicate that TPE does not consistently improve systemic vascular tone or reverse vasoplegia.

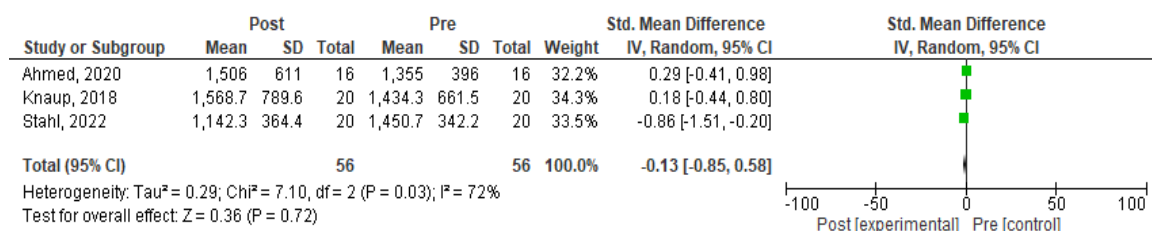


Figure 8. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on SVRI.

Stroke Volume Variation (SVV)

As shown in figure 9, TPE significantly reduced stroke volume variation (SMD -0.90 ; 95% CI -1.29 to -0.51 ; $p < 0.00001$), with no detected heterogeneity

($I^2 = 0\%$). This highly consistent effect suggests improved preload stability and intravascular hemodynamic status, potentially related to reduced capillary leak and restoration of endothelial integrity.

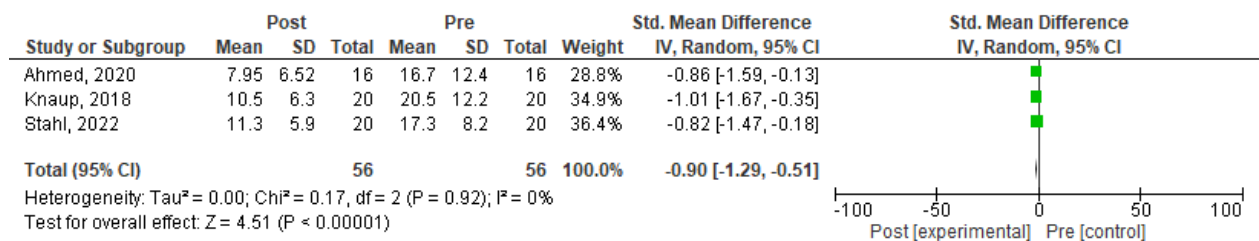


Figure 9. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on SVV.

Cardiac Index (CI)

As shown in figure 10, TPE did not significantly increase cardiac index compared with control (SMD 0.24; 95% CI -0.13 to 0.62; $p = 0.20$). No heterogeneity was observed ($I^2 = 0\%$).

Although a trend toward higher CI was noted, current evidence does not support a definitive improvement in cardiac pump function attributable to TPE alone.

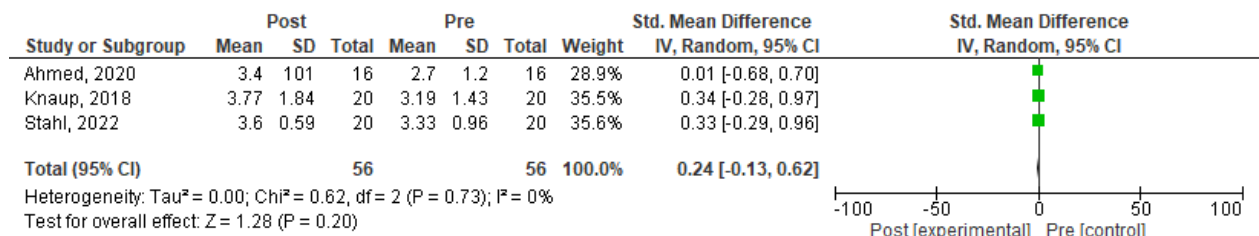


Figure 10. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on CI.

Fluid Balance and Metabolic Parameters

As shown in figure 11, TPE demonstrated a trend toward improved fluid balance compared with control (SMD -0.41; 95% CI -0.87 to 0.06; $p = 0.09$). Although this did not reach statistical significance, the

direction of effect consistently favored TPE, with no observed heterogeneity ($I^2 = 0\%$). These findings suggest a potential role of TPE in mitigating fluid overload, possibly through improved endothelial function and attenuation of systemic inflammation.

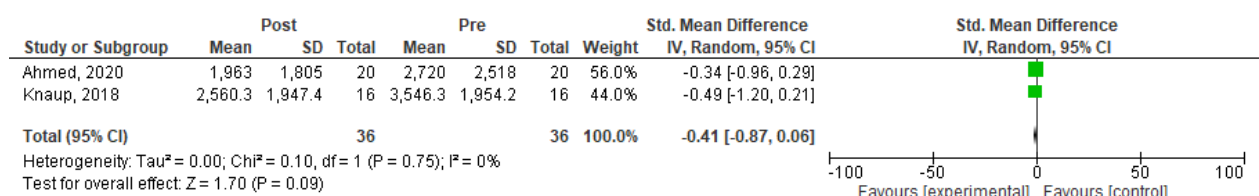


Figure 11. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on fluid balance.

As shown in figure 12, TPE did not result in a statistically significant reduction in serum lactate levels compared with control (SMD 0.06; 95% CI -0.40 to 0.53; $p = 0.78$), indicating no clear improvement in global tissue perfusion.

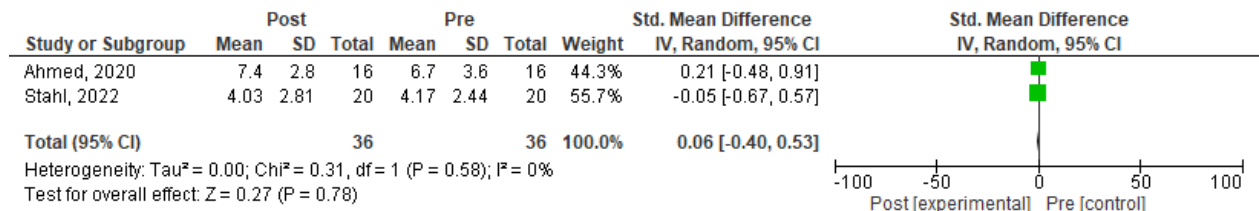


Figure 12. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on serum lactate.

Pulmonary Function

PaO₂/FiO₂ Ratio

As shown in figure 13, TPE was associated with a significant improvement in the PaO₂/FiO₂ ratio (SMD 2.41; 95% CI 0.22 to 4.61; $p = 0.03$), reflecting enhanced pulmonary oxygenation. However, heterogeneity was extremely high ($I^2 =$

96%), likely attributable to differences in patient characteristics, disease severity, timing of TPE administration, and ventilatory strategies. This finding suggests that TPE may confer pulmonary benefits through modulation of systemic inflammation and endothelial dysfunction in selected patient populations.

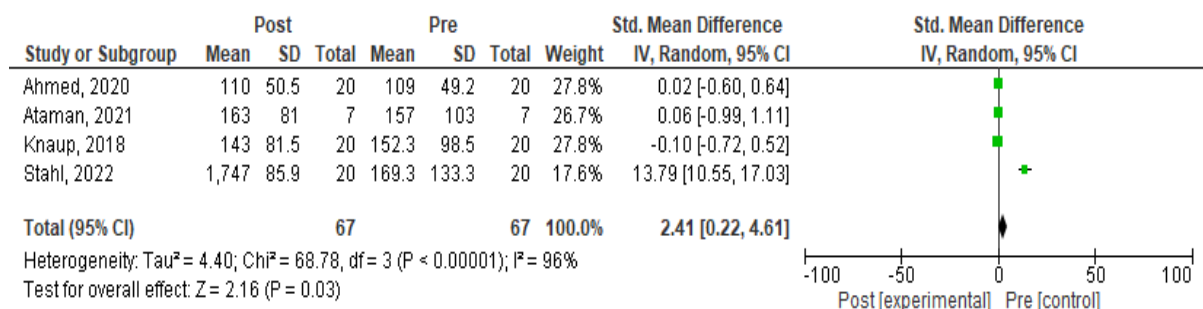


Figure 13. Forest plot of the effect of therapeutic plasma exchange (TPE) alone on PaO₂/FiO₂ Ratio

Therapeutic Plasma Exchange (TPE) Versus High-Volume Hemofiltration (HVHF)

Mean Arterial Pressure (MAP)

In subgroup analysis as shown in figure 14, TPE did not result in a significant

improvement in mean arterial pressure (MAP) (SMD 0.25; 95% CI -0.18 to 0.68; $p = 0.25$), with no observed heterogeneity ($I^2 = 0\%$). In contrast, HVHF was associated with a significant increase in MAP (SMD 1.19; 95% CI 0.31 to 2.07; p

= 0.008), although this finding was derived from a single study. There was no statistically significant difference in treatment effect between TPE and HVHF (p for subgroup difference = 0.06).

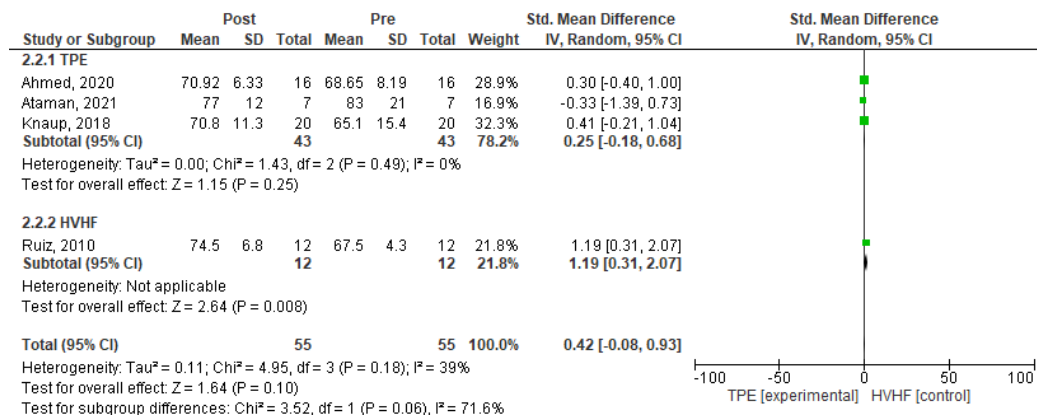


Figure 14. Forest plot comparing the effects of therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF) on mean arterial pressure (MAP).

Norepinephrine (NE) Dose

As shown in figure 15, TPE significantly reduced norepinephrine requirements compared with control (MD -0.21; 95% CI -0.27 to -0.14; $p < 0.00001$), although substantial heterogeneity was present ($I^2 = 85\%$). HVHF demonstrated a greater reduction in norepinephrine dose (MD

-0.50; 95% CI -0.71 to -0.30; $p < 0.00001$), with very high heterogeneity ($I^2 = 95\%$). Subgroup analysis revealed a statistically significant difference between TPE and HVHF (p for subgroup difference = 0.006). However, this represents an indirect subgroup comparison and should not be interpreted as evidence of superiority.

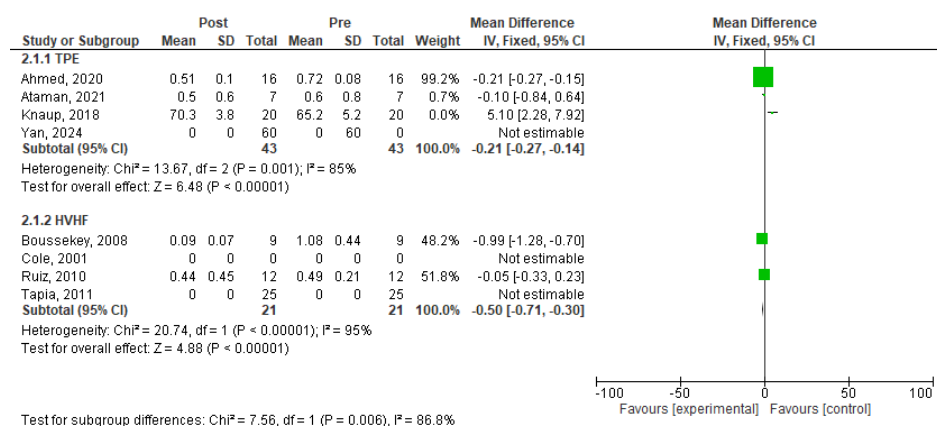


Figure 15. Forest plot comparing the effects of therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF) on norepinephrine dose

Therapeutic Plasma Exchange (TPE) Versus Standard of Care (SOC)

ICU-Free Days

As shown in figure 16, TPE did not significantly increase ICU-free days compared with SOC (MD -1.07 days; 95% CI -3.65 to

1.50; $p = 0.41$). No heterogeneity was observed ($I^2 = 0\%$), indicating consistent findings. These results suggest that physiological improvements associated with TPE have not translated into shorter ICU length of stay.

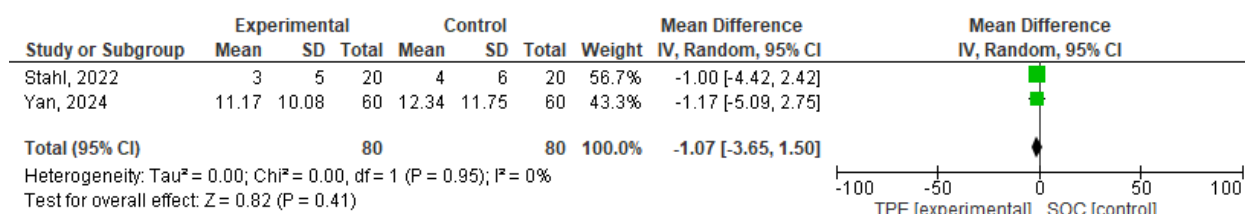


Figure 16. Forest plot of ICU-free days comparing therapeutic plasma exchange (TPE) with standard of care (SOC).

Vasopressor-Free Days

As shown in figure 17, TPE did not result in a statistically significant increase in vasopressor-free days compared with SOC (MD 2.44 days; 95% CI -0.99 to 5.87; $p =$

0.16). No heterogeneity was detected ($I^2 = 0\%$). Although a trend favoring TPE was observed, the evidence remains insufficient to demonstrate a clear clinical benefit.

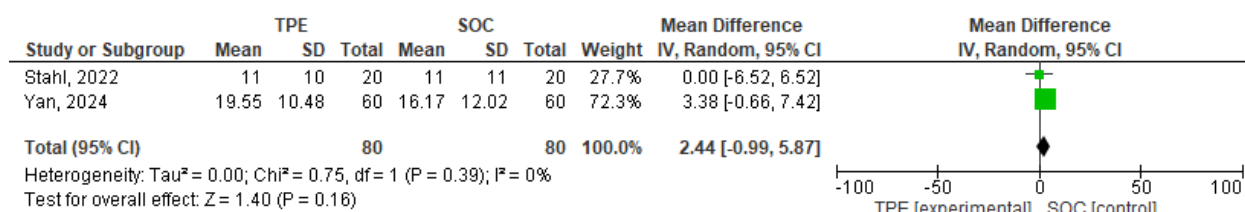


Figure 17. Forest plot of vasopressor-free days comparing therapeutic plasma exchange (TPE) with standard of care (SOC)

28-Day Mortality

As shown in figure 18, TPE was associated with a significant reduction in 28-day mortality compared with SOC (RR 0.60;

95% CI 0.47 to 0.77; $p < 0.0001$). No heterogeneity was observed ($I^2 = 0\%$), indicating highly consistent results across studies.

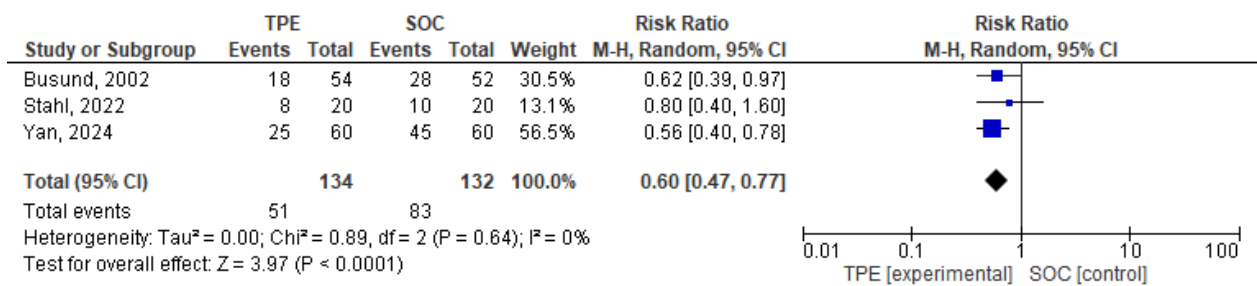


Figure 18. Forest plot of 28-day mortality comparing therapeutic plasma exchange (TPE) with standard of care (SOC).

Renal Replacement Therapy–Free Days -1.00 to 6.07 ; $p = 0.16$). No heterogeneity was observed ($I^2 = 0\%$), suggesting consistent findings. Although a trend favoring TPE was noted, current evidence does not support a definitive benefit in renal recovery.

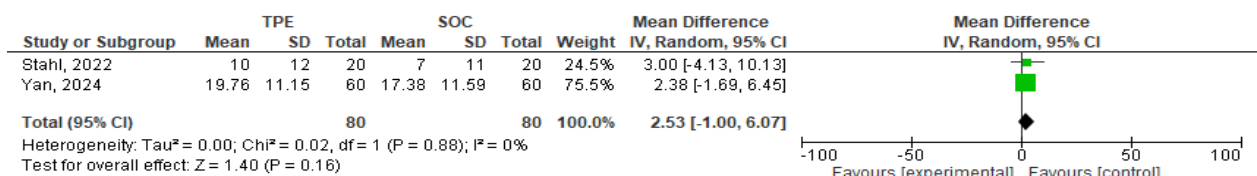


Figure 19. Forest plot of renal replacement therapy–free days comparing therapeutic plasma exchange (TPE) with standard of care (SOC).

Table 2. GRADE assessment of the certainty of evidence for major outcomes

Outcome	Effect estimate (95% CI)	Participants (studies)	Certainty of evidence	Importance	Comment
Norepinephrine dose reduction ≤ 6 h	SMD 1.06 SD lower (1.97 lower to 0.15 lower)	40 (3 studies)	$\oplus\bigcirc\bigcirc\bigcirc$ Very low ^{abc}	CRITICAL	Significant pooled early reduction; certainty limited by risk of bias, substantial heterogeneity, and indirect comparison between TPE and HVHF.
Norepinephrine dose reduction at 12 h	SMD 0.33 SD lower (0.87 lower to 0.21 higher)	27 (3 studies)	$\oplus\bigcirc\bigcirc\bigcirc$ Very low ^{acd}	CRITICAL	No statistically significant reduction; confidence interval crossed the null effect and the TPE–HVHF comparison was indirect.
Norepinephrine dose reduction at 24 h	SMD 1.54 SD lower (3.02 lower to 0.07)	35 (3 studies)	$\oplus\bigcirc\bigcirc\bigcirc$ Very low ^{abcd}	CRITICAL	Significant pooled reduction, but heterogeneity was

Outcome	Effect estimate (95% CI)	Participants (studies)	Certainty of evidence	Importance	Comment
	lower)				substantial; the HVHF estimate was derived from a single study.
ICU-free days	MD 1.07 days lower (3.65 lower to 1.50 higher)	160 (2 studies)	⊕⊕○○ Low ^{ad}	IMPORTANT	No significant improvement in ICU-free days; estimate was imprecise.
Vasopressor-free days	MD 2.44 days higher (0.99 lower to 5.87 higher)	160 (2 studies)	⊕⊕○○ Low ^{ad}	CRITICAL	Direction favored TPE, but the confidence interval included no effect.
28-day mortality	RR 0.60 (0.47 to 0.77)	266 (3 studies)	⊕⊕⊕○ Moderate ^a	CRITICAL	TPE was associated with lower 28-day mortality; no statistical heterogeneity was observed.
RRT-free days	MD 2.53 days higher (1.00 lower to 6.07 higher)	160 (2 studies)	⊕⊕○○ Low ^{ad}	IMPORTANT	No statistically significant improvement; estimate remained imprecise.

CI: confidence interval; MD: mean difference; SMD: standardized mean difference; RR: risk ratio; RRT: renal replacement therapy; TPE: therapeutic plasma exchange; HVHF: high-volume hemofiltration.

^a Downgraded one level for risk of bias because the body of evidence included non-randomized studies and randomized trials with methodological concerns.

^b Downgraded one level for inconsistency because substantial statistical heterogeneity was observed across contributing studies.

^c Downgraded one level for indirectness because comparisons between TPE and HVHF were based on indirect subgroup analyses rather than direct head-to-head trials.

^d Downgraded one level for imprecision because of small sample sizes and/or wide confidence intervals that included clinically different effects.

The certainty of evidence varied across the evaluated outcomes. Evidence for norepinephrine dose reduction at 6, 12, and 24 hours was rated as very low certainty. The certainty was downgraded because of risk of bias and indirectness, with additional concerns regarding inconsistency at 6 and 24 hours and imprecision at 12 and 24 hours. Despite their very low certainty, these outcomes were considered critical because norepinephrine

requirement was the primary hemodynamic outcome of this review.

Evidence for ICU-free days, vasopressor-free days, and RRT-free days was rated as low certainty, primarily because of risk of bias and imprecision. ICU-free days and RRT-free days were considered important outcomes, whereas vasopressor-free days were considered critical. Among the clinical outcomes, 28-day mortality had the highest certainty of evidence

and was rated as moderate. The certainty was downgraded for risk of bias, whereas no serious concerns were identified regarding inconsistency, indirectness, or imprecision. Mortality was considered a critical outcome. The complete GRADE assessment is presented in Table 2.

DISCUSSION

This systematic review and meta-analysis suggests that both therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF) are associated with reductions in norepinephrine (NE) requirements in patients with refractory septic shock, although their temporal patterns differed across the available studies. TPE was associated with early hemodynamic improvement, whereas HVHF showed a more sustained reduction in vasopressor requirements in the indirect subgroup analyses. These findings should be interpreted cautiously because direct head-to-head randomized comparisons between TPE and HVHF were unavailable.

Early Hemodynamic Response and Temporal Patterns of Vasopressor Reduction

The pooled analysis demonstrated a significant reduction in norepinephrine dose within the first 6 hours following extracorporeal therapy. In subgroup analyses, TPE was associated with a significant reduction in norepinephrine dose, whereas the pooled HVHF estimate did not reach statistical significance. A significant subgroup difference was observed between

TPE and HVHF; however, because this comparison was indirect and derived from separate studies rather than direct head-to-head randomized comparisons, it should not be interpreted as evidence of superiority of one modality over the other. These findings suggest an early overall hemodynamic response following extracorporeal therapy, although modality-specific estimates remain uncertain.^{9,10,20} At 24 hours, a significant pooled reduction in norepinephrine dose was observed. The TPE subgroup did not reach statistical significance, whereas the HVHF estimate was significant but was derived from a single study. These findings suggest possible differences in temporal response patterns; however, the indirect nature of the comparison and limited evidence precludes any conclusion regarding superiority.

Macrohemodynamics Versus Microcirculatory and Endothelial Effects

Despite its early effect on NE dose reduction, TPE did not consistently improve macrocirculatory parameters such as mean arterial pressure (MAP), MAP/NE ratio, systemic vascular resistance index (SVRI), or cardiac index. These findings suggest that the hemodynamic benefit of TPE is not primarily mediated through restoration of global vascular tone or enhancement of cardiac output.

Instead, TPE demonstrated a robust and highly consistent reduction in stroke volume variation (SVV), indicating improved preload stability and intravascular volume

responsiveness. This effect likely reflects restoration of endothelial barrier integrity and attenuation of capillary leaks which are hallmark features of septic shock–associated endothelial dysfunction. Experimental and clinical data suggest that TPE removes circulating endothelial injury mediators while simultaneously replenishing protective plasma components, thereby stabilizing the vascular barrier and improving effective circulating volume.^{9,10,20}

In addition, TPE was associated with significant improvement in pulmonary oxygenation, as reflected by increased PaO₂/FiO₂ ratios, although with substantial heterogeneity. These finding suggests that selected patient populations particularly those with pronounced inflammatory lung injury or endothelial disruption may derive pulmonary benefit from TPE, potentially through reduced alveolar-capillary permeability and mitigation of inflammatory edema.^{4,20,21}

Immunomodulation Beyond Cytokine Removal

Importantly, the effects of TPE extend beyond nonspecific cytokine clearance. TPE enables replacement of depleted plasma constituents, including antithrombin III, protein C, and other anticoagulant and endothelial-protective factors that are frequently consumed during severe sepsis and disseminated intravascular coagulation. Restoration of these factors may contribute to improved microcirculatory flow, reduced thromboinflammation, and enhanced organ

perfusion mechanisms that may not be adequately captured by conventional macrocirculatory endpoints.^{6,10,20,21}

Emerging evidence also highlights the interaction between TPE and the endothelial glycocalyx, a critical regulator of vascular permeability and mechanotransduction that is profoundly disrupted in septic shock. Prospective studies suggest that TPE may reduce circulating glycocalyx degradation products while replenishing protective plasma components, thereby limiting capillary leakage and tissue edema and contributing to early hemodynamic stabilization.^{3,10}

Clinical Outcomes and 28-Day Mortality

One of the clinically relevant findings of this meta-analysis was the association between TPE and lower 28-day mortality, with consistent effect estimates and no observed statistical heterogeneity. This association was observed despite the absence of statistically significant improvements in ICU-free days, vasopressor-free days, or renal replacement therapy–free days. However, the certainty of evidence for 28-day mortality was rated as moderate, and the pooled evidence included both randomized and non-randomized studies. Therefore, this finding should be interpreted as an association rather than definitive evidence of a causal survival benefit. The observed association with lower mortality may reflect effects extending beyond short-term hemodynamic changes, including modulation of immune dysregulation, endothelial protection, and microcirculatory function.^{6,20}

However, the available evidence does not establish these mechanisms as causal explanations for the mortality finding. Further adequately powered randomized controlled trials are required to determine whether TPE improves survival in patients with refractory septic shock.

HVHF was associated with a more sustained vasopressor reduction in indirect subgroup analyses. Prior meta-analyses and narrative reviews have shown that HVHF may improve selected hemodynamic or metabolic parameters, yet has not consistently translated into a mortality reduction when compared with standard care, underscoring the importance of patient selection and timing of therapy.^{10,22,23}

Therapeutic Positioning and Precision-Based Application

Taken together, the available evidence suggests that TPE and HVHF may have different hemodynamic profiles in refractory septic shock. HVHF was associated with more sustained vasopressor reduction in the available studies, whereas TPE was associated with earlier hemodynamic changes and selected microcirculatory and pulmonary effects. However, the absence of direct head-to-head randomized trials precludes definitive conclusions regarding the relative clinical effectiveness or optimal positioning of either modality. Further randomized studies are required to determine whether specific patient phenotypes derive greater benefit from one extracorporeal strategy than another.²⁴⁻²⁶ Rather than viewing these modalities as

mutually exclusive, our results suggest that TPE and HVHF occupy distinct but complementary therapeutic niches, and sequential or combined strategies warrant further investigation.

Limitations

Several limitations should be acknowledged. Most included studies were observational, introducing potential selection bias and residual confounding. Heterogeneity in patient populations, timing of intervention, dosing protocols, and outcome definitions limits the generalizability of pooled estimates. Direct head-to-head randomized comparisons between TPE and HVHF were lacking, necessitating indirect subgroup analyses. Finally, data on long-term functional outcomes and quality of life remain sparse. The GRADE assessment further indicated that certainty of evidence ranged from very low to moderate across outcomes. Certainty was particularly limited for hemodynamic comparisons because of heterogeneity, imprecision, and the indirect nature of comparisons between TPE and HVHF.

Future Directions

Future research should prioritize large, multicenter randomized controlled trials directly comparing TPE and HVHF using standardized definitions of refractory septic shock and harmonized outcome measures. Identification of biomarkers predictive of response, such as lactate kinetics, endothelial injury markers, or inflammatory profiles, may enable individualized therapy. Exploration of

sequential or combination extracorporeal strategies may further refine the role of blood purification in modern shock management.¹

CONCLUSION

This systematic review and meta-analysis suggests that both therapeutic plasma exchange (TPE) and high-volume hemofiltration (HVHF) are associated with reductions in norepinephrine requirements in patients with refractory septic shock. Indirect subgroup analyses suggested different temporal patterns, with TPE showing earlier reductions in vasopressor requirements and HVHF showing a more sustained effect in the available studies. TPE was also associated with improvements in selected hemodynamic and pulmonary parameters and with lower 28-day mortality. However, these findings should be interpreted cautiously because of the heterogeneity of the included studies, the limited evidence base, and the absence of direct head-to-head randomized comparisons between TPE and HVHF. Further randomized controlled trials are required to determine their comparative clinical effectiveness and optimal role in refractory septic shock.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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