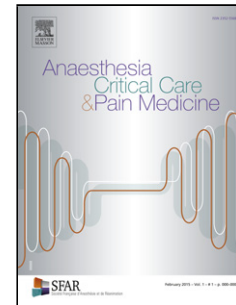


Journal Pre-proof

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PII: S2352-5568(26)00189-X

DOI: <https://doi.org/10.1016/j.accpm.2026.101931>

Reference: ACCPM 101931

To appear in: *Anaesthesia Critical Care & Pain Medicine*

Accepted Date: 15 September 2026

Please cite this article as: Abou-Arab O, Beyls C, Ibrahima A, Appa A, Alshatri HY, Colombel J, Kamel S, Moussa MD, Besnier E, Saleh K, Mahjoub Y, Mallat J, Hemoadsorption to prevent acute kidney injury in elective cardiac surgery: a systematic review of randomized controlled trials with meta-analysis and trial sequential analysis, *Anaesthesia Critical Care and Pain Medicine* (2026), doi: <https://doi.org/10.1016/j.accpm.2026.101931>

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Hemoadsorption to prevent acute kidney injury in elective cardiac surgery: a systematic review of randomized controlled trials with meta-analysis and trial sequential analysis

Running title: Hemoadsorption in cardiac surgery: a meta-analysis

Osama Abou-Arab, MD PhD¹; Christophe Beyls, MD PhD¹; Azrat Ibrahima, MD¹; Arvind Appa, MD²; Hamza Yaha Alshatri, MD¹; Juliette Colombel, MD¹; Said Kamel, MD PhD³; Mouhamed Djahoum Moussa, MD PhD⁴; Emmanuel Besnier, MD PhD⁵; Khaled Saleh, MD⁶; Yazine Mahjoub, MD PhD¹; Jihad Mallat, MD PhD^{7,8,9}

¹ Department of Anesthesia and Critical Care, Amiens University Hospital, F-80000 Amiens, France

² Department of Cardiac Surgery, Amiens University Hospital, F-80000 Amiens, France

³ EA 5717, MP3CV, CURS, Université de Picardie Jules Verne, F-80000 Amiens, France

⁴ Department of Anesthesiology and Critical Care Medicine, CHU Lille, F-59000 Lille, France

⁵ Department of Anesthesiology and Critical Care, University of Rouen Normandy, INSERM EnVI UMR 1096, CHU Rouen, F-76000 Rouen, France

⁶ Respiratory Division, Integrated Hospital Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

⁷ Critical Care Division, Integrated Hospital Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

⁸ Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA

⁹ Faculty of Medicine, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Address for correspondence

Prof. Osama Abou-Arab, MD, PhD

Anesthesia and Critical Care Department, Amiens University Medical Center, 1 rue du Professeur Christian Cabrol, 80054 Amiens, France.

E-mail: osama.abouarab@gmail.com

Tel.: +33 3 22 08 78 36

Abstract

Background: This meta-analysis aimed to evaluate whether intraoperative hemoadsorption during cardiopulmonary bypass (CPB) improves postoperative outcomes compared with the standard of care.

Methods: We systematically searched EMBASE, PubMed, and the Cochrane Library for randomized controlled trials (RCTs) comparing hemoadsorption versus standard care in patients undergoing cardiac surgery with CPB. Data were analyzed using a frequentist approach and trial sequential analysis (TSA). The primary outcome was the incidence of cardiac surgery–associated acute kidney injury (CSA-AKI) within 7 days after surgery. The protocol was prospectively registered in PROSPERO (CRD42025634991).

Results: A total of six RCTs comprising 798 patients were included. Four RCTs ($n = 723$; 355 hemoadsorption, 368 control) reported CSA-AKI incidence, which did not significantly differ between groups ($RR = 0.93$ [95% CI: 0.71–1.21], $p = 0.57$; $I^2 = 42.0\%$). Hemoadsorption was not associated with significant differences in secondary outcomes: interleukin-6, tumor necrosis factor, 28-day mortality, SOFA score, and ICU length of stay.

Conclusion: Hemoadsorption during CPB was not associated with a reduction in CSA-AKI or with improvement in secondary clinical outcomes in elective patients undergoing cardiac

surgery. However, the accrued sample represented only 48% of the heterogeneity-adjusted required information size (1,491 patients), and the cumulative Z-curve crossed neither the monitoring nor the futility boundary.

Registration: PROSPERO International Register of Systematic Reviews (CRD42025634991; January 31, 2025)

Keywords: hemoadsorption; cardiac surgery; cytokine; meta-analysis; acute kidney injury; SIRS

Introduction

Systemic inflammatory response syndrome (SIRS) is a common occurrence following cardiac surgery and results from a multifactorial process. In many cases, SIRS has minimal clinical impact; however, in others it can progress to organ dysfunction or sepsis owing to a dysregulated inflammatory response.[1] Among the various triggers, the use of cardiopulmonary bypass (CPB) is considered a major driver, primarily through the activation of inflammatory pathways and the release of proinflammatory cytokines. [2]

Based on these observations, the role of hemoadsorption in cardiac surgery has been increasingly investigated in recent years. [3] Hemoadsorption is an extracorporeal blood-purification technique that uses a membrane made of polymers with sorbent properties.[4] It allows non-selective adsorption of various blood molecules, including cytokines. Interest in this approach has grown in cardiac surgery, driven by the hypothesis that hemoadsorption could improve patient outcomes by adsorbing intraoperative cytokines and attenuating the subsequent postoperative SIRS. [5,6]

Several recent randomized controlled trials (RCTs) have investigated whether hemoadsorption can attenuate SIRS and reduce related organ failure, particularly cardiac surgery-associated acute kidney injury (CSA-AKI). The findings have been conflicting, with only one large RCT enrolling more than 300 patients across two centers reporting a significant decrease in CSA-

AKI incidence. However, evidence remains limited, as most studies have been constrained by small sample sizes.

Moreover, the membrane type varies across studies, with most reporting two membrane types: the AN69 membrane and the Cytosorb membrane.

These devices are not equivalent. The polystyrene-divinylbenzene cartridge removes solutes by hydrophobic adsorption and size exclusion,[7] whereas the modified AN69 membrane adsorbs electrostatically,[4] carries a polyethyleneimine layer directed against endotoxin, and exerts an associated convective effect; target spectrum, binding capacity, duration of exposure and position within the circuit differ accordingly. What they share is the removal of circulating mediators by sorption within the extracorporeal circuit.

The present analysis is therefore deliberately posed at the level of the strategy rather than the device: we asked whether intraoperative sorbent-based blood purification, as currently applied in randomized trials, improves postoperative outcomes compared with standard care.

Since no meta-analysis has yet synthesized these recent findings, we aimed to enhance statistical power and assess the potential clinical benefits by pooling all published RCTs. The primary endpoint was the postoperative incidence of CSA-AKI within 7 days after surgery.

Methods

Protocol and registration

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist. [9] The protocol was prospectively registered in the PROSPERO International Register of Systematic Reviews (CRD42025634991; January 31, 2025) (Supplemental file).

Literature search strategy and eligibility criteria

We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from database inception to February 3, 2025. The search strategy combined relevant keywords and Medical Subject Headings (MeSH) terms related to hemoadsorption and CPB (Supplemental file). All RCTs comparing hemoadsorption *versus* standard care in adult patients undergoing cardiac surgery with CPB were considered eligible. Exclusion criteria included observational studies, case series, and trials in which hemoadsorption membranes were used primarily to treat endotoxemia or sepsis (Supplemental file).

PICO statement

We used the PICO framework to define the research question and inclusion criteria. Population (P): adult patients undergoing elective cardiac surgery requiring CPB, including endocarditis. Intervention (I): use of a hemoadsorption membrane during CPB. Comparator (C): standard care (no hemoadsorption) during CPB. Outcome (O): the primary outcome was the incidence of cardiac surgery-associated acute kidney injury (CSA-AKI) within 7 days after surgery,

defined according to KDIGO criteria as an increase in serum creatinine of $\geq 26.5 \mu\text{mol/L}$ from the preoperative (reference) baseline value.[10] Secondary outcomes included 28-day mortality, interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels at the end of the CPB, the Sequential Organ Failure Assessment (SOFA) score at ICU admission, and the ICU length of stay (ICU-LOS). Studies on heart transplantation and aortic dissection were excluded for multiple reasons: large baseline variation in cytokines, heterogeneous population and clinical presentation, specific postoperative course. Furthermore, studies in which AKI was defined by AKIN criteria were excluded to maintain a consistent outcome definition. [11] Observational studies were also excluded.

Study selection

Two reviewers (CB and AI) independently screened all titles and abstracts in a blinded fashion. Disagreements were resolved by a third reviewer (OAA). The same process was applied for full-text screening.

Data extraction

Data extraction was performed independently by three reviewers (OAA, AI, CB). Study characteristics (author, year, trial design, blinding, and funding), participant details (sample size, inclusion/exclusion criteria, baseline characteristics), and reported outcomes were extracted. Binary outcome data were recorded as absolute event counts and total sample sizes. Continuous outcomes were recorded as mean (standard deviation [SD]) or median (interquartile range [IQR]). Intention-to-treat (ITT) data were prioritized whenever available.

Risk-of-bias assessment

We assessed the risk of bias of each included trial using the Cochrane Risk of Bias tool 2.0 (RoB 2). [12] The RoB 2 tool evaluates five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Two independent reviewers (CB and AA) assessed the five domains, with disagreements resolved through discussion with a third author (OAA). Publication bias was assessed using contour-enhanced funnel plots and Egger's test for each outcome. [13]

Certainty of evidence

The certainty of evidence for the primary outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. [14,15] Two reviewers (AA and OAA) independently evaluated the quality of evidence, with any discrepancies resolved by consensus. Because all included studies were RCTs, the initial quality rating was considered high and subsequently downgraded when specific concerns were identified. Downgrading was based on predefined domains, including risk of bias (assessed with the RoB 2 tool), inconsistency (unexplained heterogeneity between studies), indirectness (limited applicability of findings to the target population), imprecision (small sample sizes or wide 95% confidence intervals encompassing both potential benefit and harm), and publication bias (evidence of small-study effects).

Statistical analysis

Binary outcomes were assessed using pooled risk ratios (RRs) with 95% confidence intervals (CIs), while continuous outcomes were assessed using mean differences (MDs). Owing to

anticipated clinical and methodological heterogeneity across the included studies, data were pooled using a random-effects model with the restricted maximum-likelihood (REML) estimator. Heterogeneity was quantified using the Higgins I^2 index [16] and the Cochran Q test, with significant heterogeneity defined as $p < 0.10$ and $I^2 \geq 50\%$, in accordance with the Cochrane Handbook guidelines.

For continuous variables reported as medians and interquartile ranges, means and standard deviations were estimated using the approach described by Wan *et al.* [17] to permit their inclusion in the meta-analysis. Analyses were conducted in Stata 17.0 (StataCorp LLC, College Station, TX, USA). A two-sided $p < 0.05$ was considered statistically significant. For the primary outcome, a prespecified subgroup analysis was conducted by hemoadsorption membrane type (oXiris® or CytoSorb®).

Trial sequential analysis

To evaluate the robustness of the primary outcome and minimize the risk of type I errors due to sparse data or repetitive testing, we performed trial sequential analysis (TSA) using TSA software (version 0.9.5.10 Beta; Copenhagen Trial Unit, Denmark). We constructed a cumulative Z-curve using a random-effects model, with the required information size (RIS) adjusted for heterogeneity (diversity). The analysis was based on a two-sided significance level of 5%, a power of 80%, and an anticipated relative risk reduction of 20%. The control event rate was based on the pooled incidence in the control groups. Monitoring boundaries for benefit, harm, and futility were established using the O'Brien-Fleming alpha-spending function. A conclusive result was reached if the cumulative Z-curve crossed the trial sequential monitoring boundary or entered the futility zone. If the Z-curve failed to reach the RIS or cross a boundary, the evidence was deemed insufficient to draw definitive conclusions. [18]

Results

Search results and trial characteristics

A flow diagram of the study-selection process is presented in Figure 1. The electronic database search initially identified 185 potentially relevant records. After removal of duplicates, 83 articles remained for screening. Following title and abstract screening, the full texts of 83 studies were assessed for eligibility. 29 studies that did not meet the inclusion criteria (Figure 1) were excluded: 4 studies for heart transplantation, 5 studies for septic shock, 12 studies for bleeding or antiplatelet/anticoagulant drug removal, and 12 studies for aortic repair/aortic dissection. Six RCTs comprising a total of 798 patients were included in the final analysis. [19-24]

Table 1 summarizes the characteristics of the included studies. Briefly, baseline characteristics across studies showed a similar age (around 69 years) and a predominance of male patients. The hemoadsorption setting was consistent, with strict membrane use during CPB only. The median duration of CPB varied from a minimum of 81 min to a maximum of 170 min. 5 out of the six RCTs had a median time over 100 min. The control group received standard CPB without hemoadsorption. Most of the RCTs (four) were single-center studies with small sample sizes ranging from 30 to 70 patients. [19,20,22,24] The remaining two RCTs included 288 and 343 patients, respectively. [21,23] Four RCTs used the CytoSorb® membrane and two RCTs used the AN69 (oXiris®) membrane.

Risk of bias and quality of included trials

The RoB 2 assessment indicated an overall low risk of bias in five trials (83%) and a high risk of bias in one trial (17%), primarily due to concerns about the selection of the reported result (Figure 2).

Primary outcome (CSA-AKI)

Four trials with a total of 723 patients reported the incidence of CSA-AKI. The pooled CSA-AKI rate was 44.8% (165 of 368) in the control group and 40.6% (144 of 355) in the intervention group. The use of a hemoadsorption membrane during CPB was not associated with a significant reduction in CSA-AKI compared with standard care (RR = 0.93 [95% CI: 0.71–1.21]; $p = 0.57$; $I^2 = 42.0\%$) (Figure 3).

Trial sequential analysis

The TSA for the primary outcome of CSA-AKI (Figure 4) demonstrated that the current cumulative evidence has not yet reached the heterogeneity-adjusted required information size (RIS = 1,491). The cumulative Z-curve remained well within the monitoring boundaries for benefit and harm, failing to reach the threshold for statistical significance. However, the trajectory of the Z-curve toward the futility boundary suggests that hemoadsorption is unlikely to achieve a 20% relative risk reduction in AKI compared with standard care. These findings indicate that, although more data are technically required to reach the RIS, the likelihood of a clinically meaningful treatment effect emerging in subsequent studies is low.

Subgroup analysis

A subgroup analysis was conducted to evaluate the effect of membrane type on the incidence of CSA-AKI. Two trials ($n = 411$) used the AN69 (oXiris®) membrane, while two trials ($n = 312$) used the CytoSorb® membrane. Neither membrane type was associated with a significant reduction in CSA-AKI compared with standard care. The pooled estimates were $RR = 0.88$ ([95% CI: 0.52–1.48]; $p = 0.11$; $I^2 = 60.0\%$) for oXiris® and $RR = 1.02$ ([95% CI: 0.83–1.25]; $p = 0.98$; $I^2 = 0.0\%$) for CytoSorb® (Supplemental file: eFigure 1).

Secondary endpoints

28-day mortality

Six trials with a total of 798 patients reported the incidence of 28-day mortality. The pooled 28-day mortality rate was 10.4% (41 of 393) in the control group and 9.9% (40 of 405) in the intervention group. The use of a hemoadsorption membrane during CPB was not associated with a significant reduction in 28-day mortality ($RR = 1.03$ [95% CI: 0.69–1.53]; $p = 0.88$; $I^2 = 0.0\%$) (Figure 5).

SOFA score

Four trials, including 731 patients, reported SOFA scores. The use of a hemoadsorption membrane was not associated with a significant reduction in SOFA score compared with standard care ($MD = 0.32$ points [95% CI: - 0.24 to 0.87]; $p = 0.26$), with evidence of substantial heterogeneity ($I^2 = 59.0\%$) (Supplemental file: eFigure 2).

ICU length of stay

Six trials comprising 798 patients reported ICU LOS. The use of a hemoadsorption membrane was not associated with a significant reduction in ICU LOS compared with standard care (MD

= 0.22 days [95% CI: -0.20 to 0.64]; $p = 0.30$), with no evidence of heterogeneity ($I^2 = 0.0\%$) (Supplemental file: eFigure 3).

IL-6

Six trials comprising 478 patients reported IL-6 levels after CPB. The use of a hemoadsorption membrane was not significantly associated with lower IL-6 levels compared with standard care (MD = -15.5 pg/mL [95% CI: -36.8 to 5.7]; $p = 0.15$; $I^2 = 0.0\%$) (Figure 6).

TNF- α

Five trials comprising 623 patients reported TNF- α levels after CPB. The use of a hemoadsorption membrane was not significantly associated with lower TNF- α levels compared with standard care (MD = - 0.19 pg/mL [95% CI: - 0.66 to 0.28]; $p = 0.44$; $I^2 = 0.0\%$) (Supplemental file: eFigure 4).

Publication bias and certainty of evidence

Funnel plots for all primary and secondary outcomes are presented in eFigure 5. No significant asymmetry was observed in any of the plots except for the SOFA score. Egger's tests showed no evidence of publication bias for CSA-AKI ($p = 0.70$), 28-day mortality ($p = 0.32$), ICU LOS ($p = 0.30$), IL-6 ($p = 0.42$), TNF- α ($p = 0.96$), and SOFA score ($p = 0.50$). We used the GRADE approach to assess the certainty of evidence [13]. We classified the certainty of evidence as “moderate” for the risk of CSA-AKI (Supplemental file: eTable 1).

Discussion

Key findings

In this systematic review and meta-analysis of six RCTs ($n = 798$), we compared hemoadsorption-membrane use with standard care in patients undergoing cardiac surgery with CPB. Our analysis demonstrated that hemoadsorption was not associated with a reduction in the incidence of CSA-AKI. Similarly, no significant benefits were observed for secondary outcomes, including 28-day mortality, ICU LOS, SOFA score, or circulating inflammatory markers (TNF- α and IL-6). However, the accrued sample represented less than half of the heterogeneity-adjusted required information size (723 of 1,491 patients), and the cumulative Z-curve crossed neither the monitoring nor the futility boundary. The current evidence is therefore inconclusive rather than negative: a clinically relevant reduction in CSA-AKI cannot be excluded, and adequately powered trials remain warranted.

Interpretation in light of previous literature

CSA-AKI and hemoadsorption

We selected CSA-AKI as the primary endpoint because the principal rationale for hemoadsorption is to mitigate inflammation-associated AKI. Notably, among the RCTs included in our meta-analysis, one large RCT reported a significant reduction in CSA-AKI with intraoperative hemoadsorption. [21] However, this benefit could not be confirmed when data were pooled across all included trials. Several hypotheses may explain the absence of an observed benefit on kidney outcomes. First, the extent of cytokine clearance achieved may have been insufficient to clinically attenuate inflammation-related kidney injury. Second, although CSA-AKI was consistently defined across all trials using KDIGO criteria, accurately assessing it in the early postoperative period remains challenging. This phase is characterized

by marked hemodynamic instability and ongoing therapeutic optimization, which may confound AKI diagnosis. Thus, not all cases of CSA-AKI are inflammation-driven, and a functional component may account for a substantial proportion of CSA-AKI events. Beyond relative hypovolemia, CSA-AKI is a multifactorial condition influenced by preoperative patient-related factors (such as chronic heart failure, chronic kidney disease, and diabetes) and multiple intraoperative mechanisms, including the release of nephrotoxic substances (free hemoglobin, myoglobin) and alterations in renal hemodynamics (renal vasoconstriction and hypoperfusion, hemodilution, and hypothermia).[25] Consequently, the hypothesis that CSA-AKI is primarily driven by systemic inflammation alone appears oversimplified, given the heterogeneity of its pathogenesis. Our findings diverge from those of another recent meta-analysis in cardiac surgery, which reported a significant reduction in the risk of CSA-AKI. [26] While the mentioned meta-analysis from Samaniego-Laguna *et al.* reported a reduction in the risk of CSA-AKI (RR at 0.75; 95% CI 0.59-0.96; $p = 0.020$), we could not confirm that finding in ours. When looking at some details of the analysis, the positive effect was mainly driven by SIRAKI02 and the one from Nemeth *et al.* that focused on the specific population of heart transplantation, both representing a weight over 30% of the pooled analysis. [21,27]

While observational studies suggested a clinical benefit, the significant decrease in AKI was not replicated in the RCTs; this reliance on non-randomized data likely accounts for the discrepancy in findings and underscores the importance of our RCT-based analysis in demonstrating a neutral effect on renal outcomes. [28] We also excluded reports related to plasma free hemoglobin or haptoglobin removal and those using the AKIN criteria to define AKI to avoid higher heterogeneity. [27,29,30,31]

Selection of patients with severe SIRS

The unifying rationale across the trials included in this meta-analysis was the mitigation of cytokine overproduction, which is presumed to contribute to adverse postoperative outcomes. However, the enrolled patient populations appeared to lack a high systemic inflammatory burden, as reflected by the relatively modest post-CPB cytokine levels observed in the control groups. In the broader literature, post-CPB IL-6 concentrations are typically reported to be around 400 pg/mL. While this is higher than the levels observed in our meta-analysis, it remains markedly lower than concentrations seen in conditions such as sepsis or ARDS, where the proinflammatory response is far more profound. [32,33] Consistent with this observation, recent data in cardiac surgery suggest that only markedly elevated IL-6 levels (> 1000 pg/mL) are associated with adverse outcomes. [34]

This observation of relatively low cytokine levels in the included trials may explain the absence of detectable cytokine clearance. The adsorption efficiency of hemoadsorption membranes is influenced by several factors, including baseline plasma cytokine concentration, volume of distribution, blood-flow rate, and physicochemical properties such as hydrophobicity [5,35-37]. Consequently, when circulating cytokine concentrations are low, the adsorptive capacity of these membranes may be underutilized. In addition, the use of CPB may further reduce effective plasma exposure, potentially diminishing membrane efficiency. Notably, effective cytokine removal appears to require a substantial inflammatory burden. This was demonstrated in a clinical trial involving healthy volunteers, in whom meaningful cytokine attenuation was observed only when IL-6 levels exceeded approximately 2000 pg/mL; levels far higher than those reported in the present meta-analysis. [38]

In addition to concentration-dependent effects, a temporal factor may also explain our findings. All included studies limited hemoadsorption to the intraoperative period, whereas in cardiac surgery cytokine levels may continue to rise for several hours after the cessation of CPB. [39]

Extending hemoadsorption into the postoperative period might therefore be more beneficial in patients with sustained cytokine overproduction.

Notably, some meta-analyses in sepsis have reported similar findings, demonstrating no significant effect on cytokine clearance or mortality. In those contexts, the substantial heterogeneity among septic patients, characterized by highly variable cytokine concentrations, may have compromised membrane efficiency and contributed to these neutral results. [40,41]

Immune-response dysregulation

SIRS leads to adverse outcomes primarily when immune dysregulation occurs. However, in most cases of sepsis or following major surgery, such a classical maladaptive response is not consistently observed [40]. Instead, the immune response often remains relatively balanced, without overt dysregulation between pro- and anti-inflammatory pathways.

Sepsis and septic shock are characterized by a dysregulated immune response reflecting profound immune dysfunction. [42,43] Typically, an initial hyperinflammatory phase, marked by excessive cytokine production, is often followed by a compensatory immunosuppressive phase, largely mediated by monocyte dysfunction. Recent real-world data from a cohort of 1,000 patients demonstrated that patients with the most severe phenotypes exhibited markedly reduced monocyte HLA-DR expression, which was associated with a poor prognosis. [44] Notably, in our meta-analysis, none of the included trials evaluated immune dysregulation using such immunological markers; instead, the focus was limited exclusively to the proinflammatory phase without assessing subsequent immunosuppression. These observations suggest that a precision-medicine approach to hemoadsorption (guided by comprehensive immune monitoring) may be more appropriate than its indiscriminate use.

We evaluated SOFA scores as a surrogate for the potential vasopressor-sparing effect of hemoadsorption. Although observational studies (primarily involving septic patients) have suggested reduced vasopressor requirements with hemoadsorption, we hypothesized that this

benefit would be reflected in lower SOFA scores at ICU admission. However, the REMOVE trial, which was specifically designed and adequately powered to address this hypothesis, found no difference in SOFA scores between treatment groups.[23] Consistent with these findings, our meta-analysis similarly showed no evidence of a vasopressor-sparing benefit.

Limitations

Our meta-analysis has several limitations. It included mainly RCTs with relatively small sample sizes (30–80 patients), most of which were designed as hypothesis-generating or proof-of-concept studies. Consequently, clinically robust endpoints were often reported as secondary rather than primary. To address this limitation, we performed a TSA for the CSA-AKI endpoint (Figure 4). The TSA suggested that our meta-analysis remains underpowered, requiring more than 1,000 patients to detect a 20% reduction in CSA-AKI. However, the Z-curve approached the futility boundary, suggesting that additional studies are unlikely to demonstrate a clinically meaningful benefit. [45]

Another limitation is the strict selection of studies based on the PICO. We aimed to include only RCTs with a similar design: patients scheduled for cardiac surgery under CPB. Emergency procedures such as heart transplantation, acute aortic dissection, and any rescue therapy were excluded, as the cytokine profile is completely different. [27,31] Some other studies were excluded because the reporting of outcomes such as CSA-AKI was missing or defined according to AKIN criteria, with a focus on the chelation of free hemoglobin. [29,30] We believe these reasons explain the different findings from a previous meta-analysis that concluded there was a beneficial effect of hemoadsorption. [28]

Despite these limitations, the included trials were similar in terms of study design, intervention, and outcome assessment, as reflected in the risk-of-bias assessment except for the assessment of CSA-AKI (Figure 2). Indeed, all RCTs employed a standardized intervention comparison (hemoadsorption *versus* standard care) and were published within the last ten years, ensuring

consistent CPB management aligned with current guidelines. [46] Moreover, the inclusion of two large multicenter RCTs strengthened the robustness of the analysis. Finally, statistical heterogeneity was low to negligible across outcomes, further supporting the validity of our conclusions.

Conclusion

Hemoadsorption during CPB was not associated with a reduction in CSA-AKI or with improvement in secondary clinical outcomes in the unspecific risk or selected population. However, the accrued sample represented only 48% of the heterogeneity-adjusted required information size (1,491 patients), and the cumulative Z-curve crossed neither the monitoring nor the futility boundary; the evidence therefore remains inconclusive, and adequately powered trials in well-defined populations are required. The absence of a clearly defined hyperinflammatory population may explain the lack of observed benefit associated with hemoadsorption.

Author contributions

OAA: writing of the protocol, pilot search strategy, pilot screening of articles, writing of the original draft, pilot data extraction, manuscript revision, and final manuscript approval. CB: article review, pilot data extraction. AI: protocol review, bias assessment, data review. AA: running and reporting of the search strategy and grading of evidence. HYA: reporting of the search strategy. JC: data-extraction checking. SK: data interpretation, manuscript revision. MDM: review and approval of the protocol. EB: review and approval of the protocol, manuscript revision. KS: statistical analysis. YM: protocol review, manuscript revision. JM:

protocol review, drafting and revision of the manuscript, statistical analysis. All authors approved the final version of the manuscript.

Funding

None

Ethics approval and consent to participate

No ethical approval was required for the completion of this meta-analysis. Consent to participate was not applicable.

Declaration of interest

OAA received personal fees from Medtronic®, AOP Pharma®, Viatris® and LFB®. The other authors declare that they have no conflicts of interest.

Acknowledgements

None.

Data availability

The datasets are available from the corresponding author upon reasonable request.

Consent for publication

Not applicable.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Not applicable

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

Not applicable

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Declaration of generative artificial intelligence (AI) in scientific writing

During the preparation of this work, the visual abstract was performed using the Claude® software (Anthropic, California, USA)

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Figure legends

Figure 1. PRISMA 2020 flow diagram of the study-selection process.

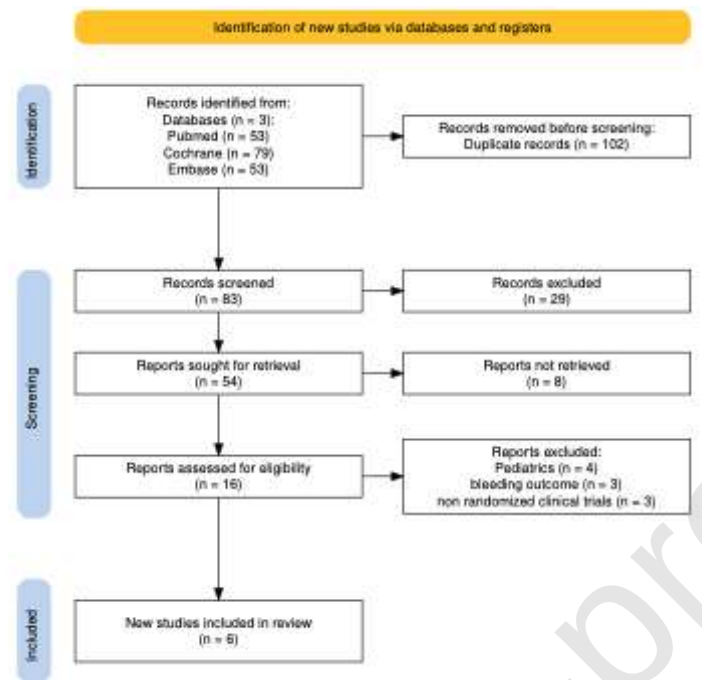


Figure 2. Risk-of-bias assessment of the included trials (Cochrane RoB 2 tool).



Figure 3. Forest plot of the primary outcome (CSA-AKI): hemoadsorption versus standard care.

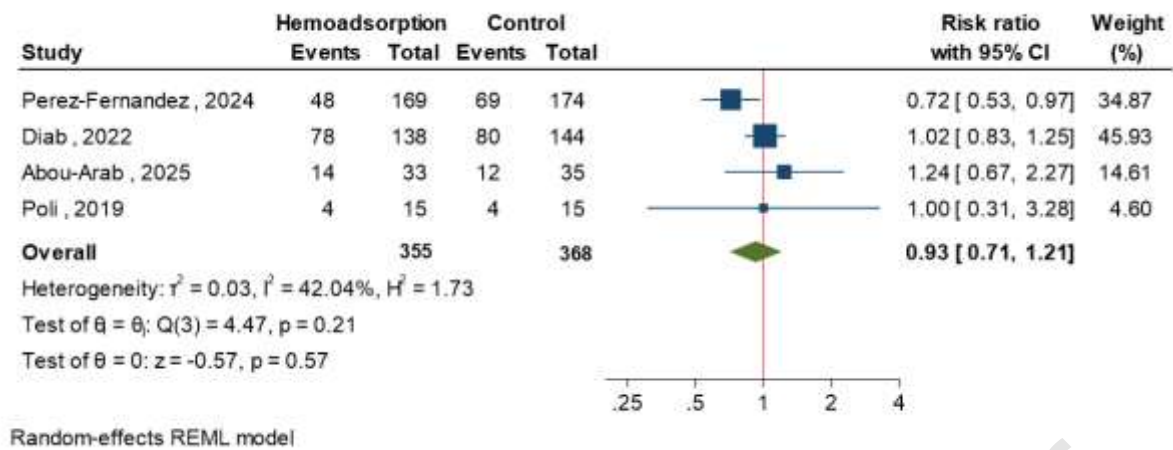


Figure 4. Trial sequential analysis for the primary outcome (CSA-AKI).

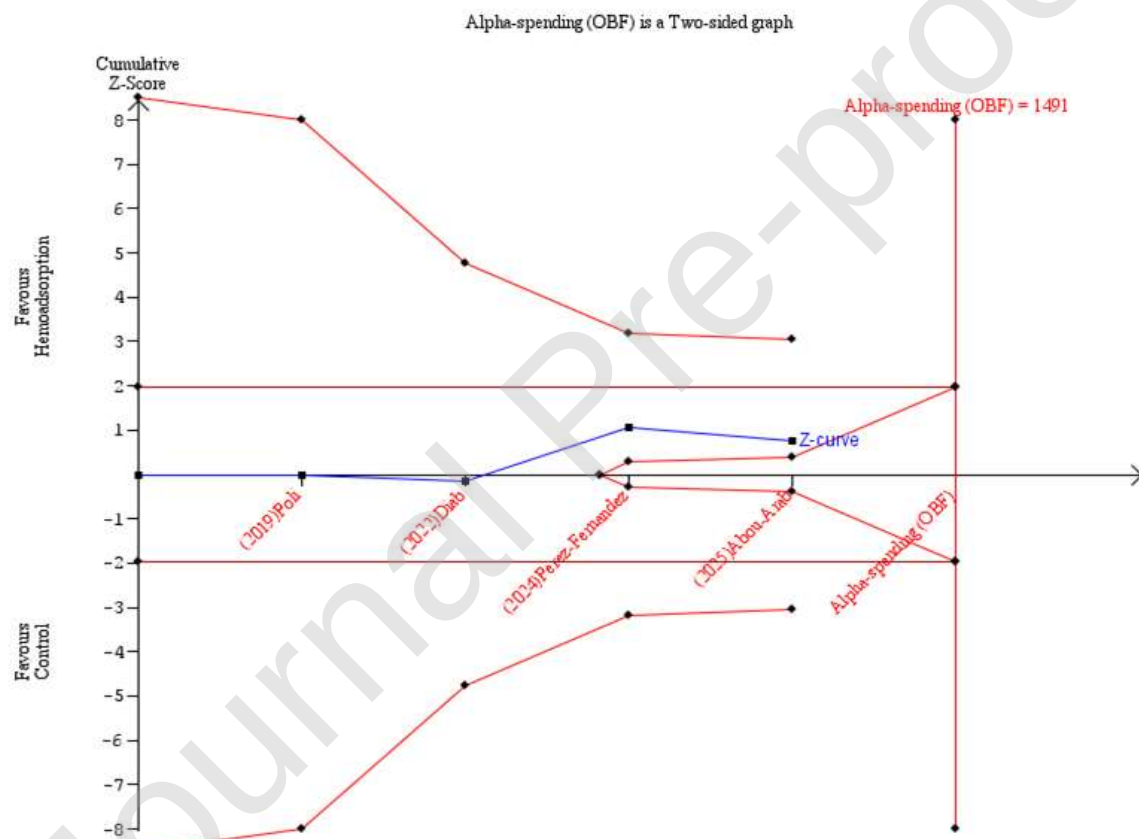


Figure 5. Forest plot of 28-day mortality: hemoadsorption versus standard care.

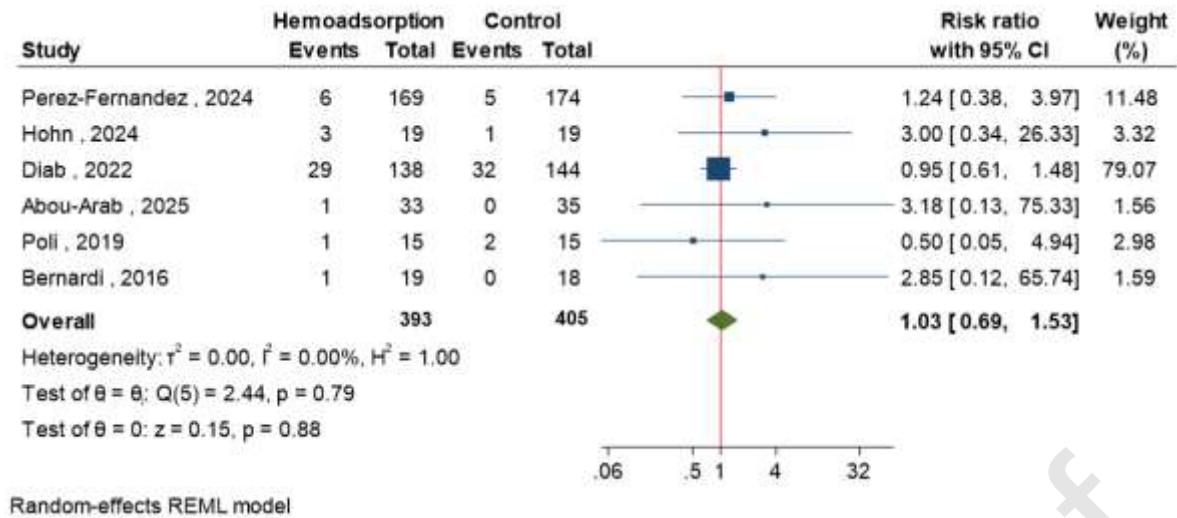


Figure 6. Forest plot of post-CPB interleukin-6 levels: hemoadsorption versus standard care.

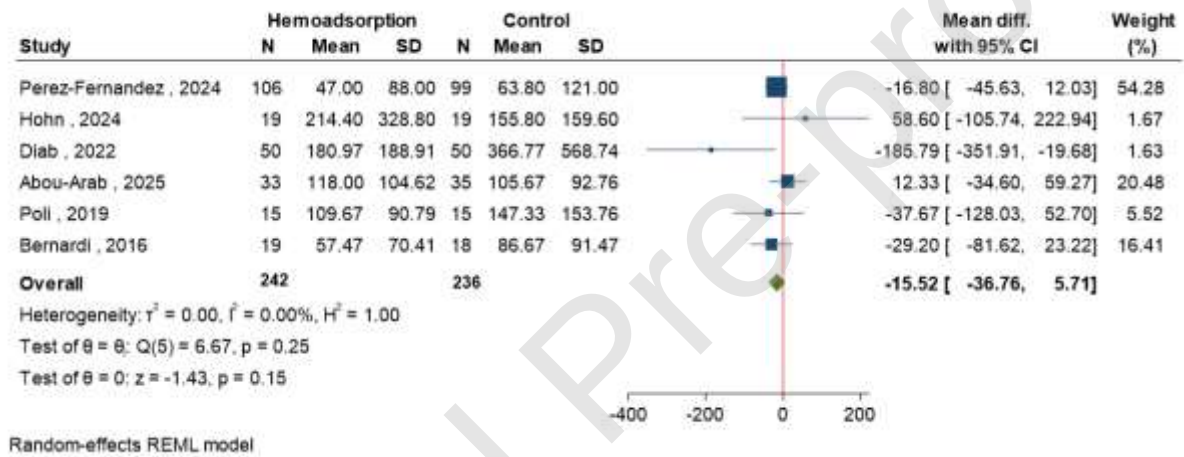


Table 1 Characteristics of included trials. CPB: cardiopulmonary bypass. NA: non-available.

Study	Bernardi <i>et al</i> 2016 [18]	Poli <i>et al</i> 2019 [19]	Pérez-Fernandez <i>et al</i> 2024 [20]	Hohn <i>et al</i> 2024 [21]	Diab <i>et al</i> 2022 [22]	Abou-Arab <i>et al</i> 2025 [23]
Participants	30	30	343	38	288	70
Inclusion criteria	46 adult patients undergoing elective cardiac surgery with CPB	Patients elected for cardiac surgery with expected long CPB duration	≥18 years old patients undergoing elective cardiac surgery with expected CPB duration > 90 min	≥65 years old patients undergoing elective cardiac surgery with CPB	Patients undergoing cardiac surgery for infectious endocarditis with CPB	≥18 years old patients undergoing elective cardiac surgery with expected CPB duration > 90 min
Exclusion criteria	Transplant surgery, scheduled insertion of a cardiac assist device, thrombendarterectomy of the pulmonary arteries, emergency and urgent procedures, serum creatinine of more than 2 mg/dl, C-reactive protein (CRP) of more than 2 mg/dl, bilirubin of more than 2 mg/dl, BMI < 18 kg/m ² , pregnancy, history of stroke, and patients receiving chemotherapy, anti-leukocyte drugs, TNF-α blockers, immunosuppressive drugs or with any diagnosed disease state that has produced leukopenia	End-stage renal disease, active infectious endocarditis, emergency or off-pump procedure, receipt of non-steroidal anti-inflammatory medication	Immunosuppressive or corticosteroid treatment, involvement of an active autoimmune disease, transplant carrier, chronic kidney disease, administration of RRT during the last 90 days, intolerance to the components of different health products, participation in another clinical trial with medications	< 65y, withdrawal of consent, emergency surgery, planned CPB temperature < 32 °C, acute infective endocarditis, AIDS, pre-existing kidney disease, prior kidney transplant application of contrast medium on day of surgery, immunosuppressive therapy, participation in another	Euroscore ≤ 3, pregnancy, or immunosuppressive or immunomodulatory therapy	<18 yr old, planned hypothermia less than 32°C, emergency surgery, active endocarditis, immunosuppressive treatment or steroids, human immunodeficiency virus infection, autoimmune disease, transplant recipient, advanced CKD, RRT within 90 days before surgery, known allergy to the device, history of heparin-induced thrombocytopenia, and coexisting illness with a high probability of death

				r clini cal inter vention		
Baseline characteristics (control group)	Age: 69 years Female: 22 % Euroscore II: 4 % Duration CPB: 170 min	Age: 69 years Female: 27 % Euroscore II: 2.5 % Duration CPB: 135 min	Age: 69 years Female: 36 % Euroscore II: 2.2% Duration CPB: 127 min	Age: 75 years Female: 32 % Euroscore II: NA Duration CPB: 163 min	Age: 69 years Female: 23 % Euroscore II: 20% Duration CPB: 81 min	Age: 68 years Female: 23 % Euroscore II: 1.0 % Duration CPB: 128 min
Baseline characteristics (hemoadsorption group)	Age: 64 years Female: 37 % Euroscore II: 6.0 % Duration CPB: 191 min	Age: 67 years Female: 20 % Euroscore II: 3 % Duration CPB: 143 min	Age: 69 years Female: 33 % Euroscore II: 2.6% Duration CPB: 132 min	Age: 74 years Female: 43 % Euroscore II: NA Duration CPB: 316 min	Age: 69 years Female: 29 % Euroscore II: 19% Duration CPB: 88 min	Age: 68 years Female: 24 % Euroscore II: 1.2 % Duration CPB: 127 min
Study design	Single center in Austria	Single center in Switzerland	Multi center (2 centers in Spain)	Single center in Germany	Multi center in Germany (14 centers)	Single center in France
Intervention	- Hemoadsorption : Cytosorbent membrane use during CPB - Control: CPB without membrane use	- Hemoadsorption : Cytosorbent membrane use during CPB - Control: CPB without membrane use	- Hemoadsorption : AN69 membrane use during CPB - Control: CPB without membrane use	- Hemoadsorption : Cytosorbent membrane use during CPB - Control: CPB without membrane use	- Hemoadsorption : Cytosorbent membrane use during CPB - Control: CPB without membrane use	- Hemoadsorption : AN69 membrane use during CPB - Control: CPB without membrane use
Primary endpoint	Difference in cytokines within 5 days after surgery	Difference in cytokines anesthesia at induction, at the end of CPB, as well as 6 and 24 h post-CPB initiation	Incidence of acute kidney injury	Difference in interleukin-6 difference at ICU admission	SOFA variation from basal to 9 th day after surgery	Sublingual microcirculation at day 1
Overall risk of bias (Rob-2)	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk

Study dates	September 2013- May 2015	May 2016 - January 2018	June 2016 - November 2021	January 2015 - February 2019	January 2018 - January 2020	October 2019 - November 2022
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