Review Article (Systematic Review and Meta-Analysis)

Effect of Albumin Concentration and Timing on Acute Kidney Injury After Adult Cardiac Surgery: A Systematic Review and Meta-analysis

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ABSTRACT

The effect of hyperoncotic (20%–25%) human albumin on cardiac-surgery–associated acute kidney injury (CS-AKI) is uncertain. This study evaluated whether intraoperative or postoperative administration of 20%–25% albumin influences the risk of CS-AKI compared with crystalloids or iso-oncotic (4%–5%) albumin. Systematic review and meta-analysis of randomized controlled trials (RCTs) and risk-adjusted cohort studies were conducted. Risk ratios (RRs) were pooled using random-effects models. Literature search of PubMed, Embase (Ovid), and Cochrane CENTRAL was carried out from January 1, 1995, to July 17, 2025. Adults undergoing on-pump CS. Four eligible studies—two RCTs and two cohort studies, encompassing 6651 patients—were included. About 20%–25% of human albumin was administered either intraoperatively or within 24 h postoperatively. Comparators were crystalloids or 4%–5% albumin. The primary outcome was the incidence of any-stage AKI within 7 days of surgery. Pooled analysis showed 20%–25% albumin increased the risk of CS-AKI (RR 1.10, 95% confidence interval [CI] 1.05–1.16; I^2 =0%). Restriction to RCTs yielded a similar result (RR 1.12, 95% CI 1.04–1.20). The increased risk was consistent for both intraoperative (RR 1.09) and postoperative (RR 1.12) administration, but the interaction between infusion timing was non-significant (P = 0.59). Infusion of 20%–25% albumin is associated with a modest but consistent increase in postoperative AKI, independent of infusion timing from intraoperative to postoperative within 24 h. Until adequately powered trials resolve the remaining imprecision, routine perioperative administration of hyperoncotic albumin should be approached with caution.

Keywords: Acute kidney injury, albumin, cardiac surgery, cardiopulmonary bypass, hyperoncotic solutions, meta-analysis

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INTRODUCTION

Acute kidney injury (AKI) after cardiac surgery (CS) is common and contributes to increased morbidity, mortality, and resource utilization.[1] Even small postoperative rises in serum creatinine independently predict worse outcomes,[2] and the incidence of CS-associated AKI (CS-AKI) ranges from approximately 5% to 40% depending on definitions and patient factors.[3,4] Preventive strategies include optimizing hemodynamics, avoiding nephrotoxic agents, and carefully selecting perioperative fluids.[1] Human serum albumin (HSA) solutions are widely used for cardiopulmonary bypass (CPB) priming and postoperative volume resuscitation. Iso-oncotic 4%–5% albumin was traditionally believed to reduce edema and preserve colloid osmotic pressure;[5] however, a large, randomized

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trial albumin in cardiac surgery (ALBICS) showed no renal benefit and increased bleeding when 4% albumin was compared with crystalloids.[6]

Interest has recently shifted to hyperoncotic albumin (20%–25%) because smaller volumes can expand plasma volume and achieve negative fluid balance. Clinicians use 20% albumin in the intensive care unit (ICU) for shock management or hypoalbuminemia,[7,8] and some anesthesiologists include it in the CPB prime.[9] The theoretical advantages include less interstitial edema and improved hemodynamics, particularly in hypoalbuminemic patients.[10,11] A small trial of preoperative 20% albumin in off-pump coronary surgery reported a halving of postoperative AKI among hypoalbuminemic patients,[12] suggesting potential renal protection in selected cases. Conversely, hyperoncotic colloids may exert nephrotoxic effects by increasing intravascular oncotic pressure, reducing glomerular filtration, and exposing renal tubules to high-protein loads.[13,14] Observational studies in critical care have linked 20%–25% albumin to increased AKI, similar to the nephrotoxicity seen with synthetic colloids.[15-19] Professional guidelines from the European Society of Anesthesiology and Intensive Care, the European Association for CardioThoracic Surgery, the Japanese Society of Anesthesiologists (JSA), and the Australian and New Zealand Intensive Care Society now recommend against routine albumin priming in CPB and advocate restrictive use of HSA after surgery.[9,20,21]

Clinical decisions about albumin use in CS often consider preoperative serum albumin concentration, baseline kidney function (usually estimated glomerular filtration rate [eGFR]), and specific hemodynamic indications such as hypotension, vasoplegia, or suspected capillary leak that persists despite balanced crystalloid resuscitation.[10-12,22] Albumin may prevent CS-AKI by maintaining plasma oncotic pressure and microvascular flow and by binding endogenous and exogenous toxins.[10,11] It also has antioxidant and endothelial-stabilizing properties.[10,11] In contrast, large oncotic loads may lower transglomerular filtration pressure and increase tubular exposure to filtered protein, which can promote kidney injury.[13,14] Contemporary perioperative guidelines therefore emphasize bundle-based AKI prevention—hemodynamic optimization, avoidance of nephrotoxins, and careful fluid selection—rather than routine albumin administration as a single renoprotective therapy.[1,9,22]

Given these conflicting data, we performed a systematic review and metaanalysis to determine whether hyperoncotic albumin (20%–25%) administered intraoperatively or postoperatively influences the risk of CSAKI. We hypothesized that 20% albumin increases AKI relative to crystalloids or 4%–5% albumin and that the effect would be consistent regardless of the timing of administration. Our secondary aims were to explore effects on AKI severity (Stage 1 vs. Stage 2–3), examine randomized trials separately, and perform a trial sequential analysis (TSA) to assess the conclusiveness of available evidence.

METHODS

Study design and eligibility criteria

We conducted a systematic review and meta-analysis in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020.[23] Studies were eligible if they met the following population, intervention, comparator, outcomes, and study design (PICOS): P—adult (≥18 years) patients undergoing on-pump CS, including coronary artery bypass grafting, valve surgery, or aortic surgery with CPB duration ≥60 min; I—20%–25% human albumin administered intraoperatively (CPB priming or infusion before CPB separation) or postoperatively (within 24 h of surgery); C—crystalloid-based priming/resuscitation or 4%–5% albumin; O—incidence of AKI (any stage) within 7 days postoperatively using Kidney Disease: Improving Global Outcomes (KDIGO) criteria (or Acute Kidney Injury Network [AKIN]/risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) if KDIGO not reported);[24,25] S—parallel-group randomized controlled trials (RCTs) and risk-adjusted cohort studies published from 1995 onwards. Exclusion criteria were off-pump surgery, pediatric populations, lack of a comparison group, non-availability of AKI outcomes, or duplicate reporting.

Protocol and registration

A prespecified protocol was registered with international prospective register of systematic reviews (PROSPERO) (CRD420251090555) before data extraction and was followed throughout the review.

Literature search

A medical librarian searched PubMed, Embase (Ovid), and the Cochrane Central Register of Controlled Trials from January 1, 1995, to July 17, 2025, using terms for CS, CPB, albumin (4%, 5%, 20%, 25%), and AKI (KDIGO, AKIN, RIFLE). We applied filters for human adults, and there were no language restrictions [eTable 1]. Search results were exported to Zotero (v6.0, a citation manager of the Corporation for Digital Scholarship) for reference management. Reference lists of eligible articles and

relevant reviews were manually screened. Title/abstract and full-text screening were managed in Rayyan (QCRI). Three reviewers worked independently, and conflicts were resolved by discussion. Rayyan's automation/machine-learning suggestions were not used to make inclusion decisions.

Data extraction

Two reviewers independently extracted data using a piloted, standardized form, and a third reviewer verified all entries; discrepancies were resolved by consensus. Data were transcribed into a prespecified Excel spreadsheet mirroring Table 1, including study design, sample size, age, gender, baseline renal functions (serum creatinine and eGFR), baseline serum albumin levels, comorbidities (hypertension and diabetes), and EuroSCORE. Other additional characteristics, including operative data, AKI definition, and AKI rate, were summarized in Supplemental eTable 2. No additional author contacts or supplemental data requests were undertaken. Where only proportions were reported, event counts were back-calculated from denominators. Continuous variables reported as medians and interquartile ranges were converted to estimated means and standard deviations using the method described by Wan *et al.*[26] This estimation was applied to the studies by Balachandran *et al.*, Wigmore *et al.*, and Zhang *et al.* Furthermore, for the study by Zhang *et al.*, which reported data across multiple propensity-matched subgroups, we calculated the pooled mean and standard deviation by combining the subgroup estimates weighted by their respective sample sizes. KDIGO definitions were prioritized; where AKIN or RIFLE were reported, thresholds were harmonized to KDIGO categories when feasible.

Risk of bias assessment

Risk of bias for RCTs was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool,[27] with judgments categorized as low, some concerns, or high based on the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For cohort studies, the ROBINS-I tool was used,[28] with judgments of low, moderate, serious, or critical risk based on confounding, selection bias, classification of interventions, deviations, missing data, outcome measurement, and reporting. Disagreements were resolved by consensus.

Statistical analysis

For each study, we calculated or extracted the risk ratio (RR) for AKI comparing the albumin group with the control group. When necessary, odds ratios were approximated to RRs. For RCTs, we preferentially used stratified or adjusted RRs when

Table 1: Study characteristics

Study ID	Group	Design	Sample size	Age (±SD)	Gender, Male (%)	Baseline renal function		Baseline serum albumin (g/L)	Comorbidities
						Serum creatinine (mg/dL)	eGFR (ml/min/1.73 m²)		Hypertension, *n* (%)
Khademi_2023	Intervention	Retrospective	260	57.6±7.5	82	0.9±0.19	78.55±30.04	4.23±1.21	90 (34.6)
	Control	cohort	246	55.7±8.3	84	1±0.19	81.39±28.93	5.86±2.63	70 (28.5)
Zhang_2025	Intervention	Retrospective	2541	59.06±3.55	65.28	0.95±0.19	NR	39.08±2.50	1286 (50.6)
	Control	cohort (PSM)	2541	58.85±3.55	65.68	0.94±0.21	NR	39.06±2.51	1276 (50.2)
Balachandran_2025	Intervention	Parallel RCT	307	69.1± 11.0	70.7	1.13±0.38	61± 16.7	37.2±4.7	229 (74.6)
	Control		304	68.9± 10.6	74.7	1.17±0.42	59.4±17.7	36.4±5.4	223 (73.4)
Wigmore_2025	Intervention	RCT secondary	224	66.25±2.71	79	0.87±0.21	83.0±21.50	37±3.71	NR
	Control	analysis	228	66.75±2.34	79	0.85±0.24	81.0±24.46	38.0±5.19	NR

SD = Standard deviation, eGFR = Estimated glomerular filtration rate, PSM = Propensity score matching, RCT = Randomized controlled trial

reported. For non-randomized studies, we extracted the most fully adjusted effect measure; when only crude data were available, we computed unadjusted RRs from 2 × 2 tables. We pooled effect estimates using a random-effects model, employing the generic inverse-variance method implemented in the meta package for R. The metagen function combines log-transformed effect sizes and their standard errors, and performs both common- and random-effects meta-analysis using inverse variance weights.[29] Between-study heterogeneity was quantified by the I^2 statistic and τ^2 restricted maximum likelihood (REML).[30] Prediction intervals for the true effect in a new study were calculated.[31]

We synthesized studies reporting comparable AKI definitions within a 7-day window and required at least two studies per synthesis. Study selection is depicted in a PRISMA 2020 flow diagram; study characteristics are tabulated, risk-of-bias summaries are presented graphically, and forest plots are displayed for both per-study and pooled effects.

Two prespecified secondary analyses were performed: (1) pooling only RCTs, and (2) subgroup comparison of intraoperative vs. postoperative albumin administration using random-effects meta-regression. An additional analysis restricted to Stage 1 AKI was undertaken to incorporate all eligible datasets. For multiple secondary comparisons, *P*-values were adjusted by the Benjamini–Hochberg false discovery rate (FDR) procedure.[32]

To examine whether the cumulative evidence was sufficient, we conducted a frequentist TSA using the R package of 'Trial Sequential Analysis' for Error Control and Inference in Sequential Meta-Analyses (RTSA). The RTSA function implements TSA to design and analyze sequential meta-analyses; we used the analysis mode with outcome set to RR and specified event counts (eI, eC) and sample sizes (nI, nC) from each study. The control event rate was estimated from pooled control groups, and a relative risk reduction of 20% was used to calculate the required information size (RIS). Sequential monitoring boundaries based on O'BrienFleming spending functions were applied to test whether the cumulative Zstatistic crossed thresholds for benefit, harm, or futility.[33] We planned to examine small-study effects using funnel plots and Egger's test when ≥10 studies were available for an outcome; with fewer studies, these analyses were not undertaken. In addition, we planned an exploratory study-level meta-regression using mean baseline eGFR; however, kidney function metrics were inconsistently reported across eligible studies, precluding a reliable meta-regression. All analyses were performed in R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

To enhance reproducibility, a co-author independently reproduced the primary meta-analysis and key secondary analyses in R using the extracted dataset and the prespecified analytic approach, confirming numerical consistency of the results.

RESULTS

Study selection and characteristics

The search yielded 127 records; seven full-text articles were assessed, and four studies met the inclusion criteria. Figure 1 shows the PRISMA flow diagram. Two were RCTs (ALBICS-AKI and HAS FLAIR II secondary analysis) [34,35] and two were retrospective cohorts.[36,37] The RCTs included 1063 patients; both tested postoperative 20% albumin versus crystalloid-based care. The ALBICS-AKI trial included high-risk patients and administered 300 mL of 20% albumin over 15 h starting within 6 h post-surgery.[34] The HAS FLAIR-II (20% Human Albumin Solution Fluid Bolus Administration Therapy in Patients after Cardiac Surgery-II) analysis evaluated 20% albumin boluses for hemodynamic support in the ICU.[35] The cohort studies examined intraoperative 20% albumin: one large propensity-matched Chinese study of 2541 pairs (Zhang *et al*.) and a smaller Iranian cohort (Khademi *et al*.) with 506 patients receiving 50 mL 20% albumin in the CPB prime.[36,37] All studies defined AKI using KDIGO or AKIN criteria.[24,25]

Baseline demographic and clinical characteristics are summarized in Table 1 and eTable 2. Across included studies, patient risk profiles varied, including differences in age, comorbidities (e.g., hypertension and diabetes mellitus where reported), baseline kidney functions (serum creatinine/eGFR), baseline albumin levels, and operative risk metrics (e.g., EuroSCORE when available). Baseline kidney function was reported inconsistently, and therefore, we could not perform the prespecified exploratory meta-regression assessing effect modification by baseline eGFR.

Risk of bias was assessed using RoB 2 for randomized trials and risk of bias in non-randomized studies - of interventions (ROBINS-I) for observational cohorts. Both randomized trials were judged as having some concerns overall, mainly driven by concerns in the randomization process and/or selection of the reported results. In contrast, the observational cohort studies had a higher risk of bias (moderate to serious overall), primarily due to confounding by indication and, in one cohort, additional concerns related to participant selection and missing data [Table 2]. These limitations are inherent to non-randomized treatment allocation and should be considered when interpreting pooled estimates.

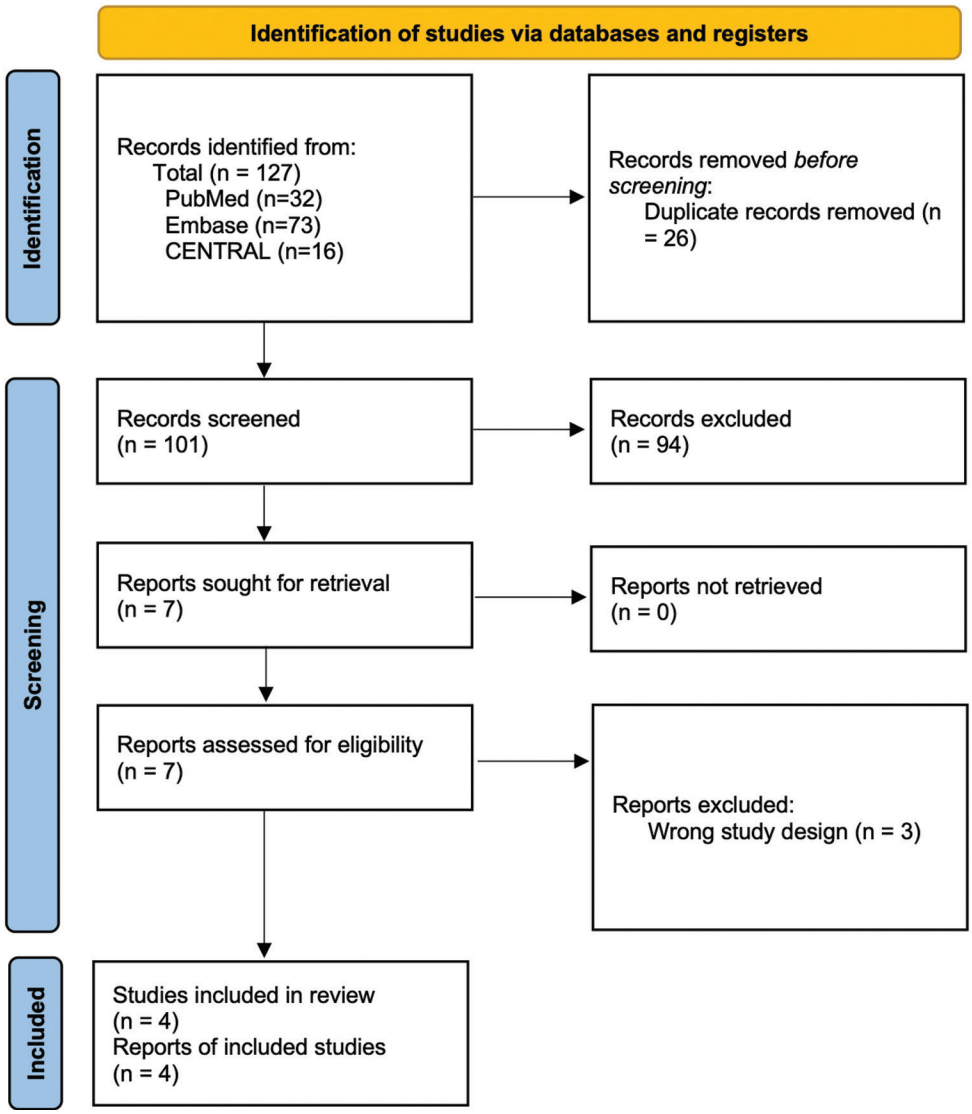

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 flow diagram. Study identification, screening, and inclusion for the meta-analysis. RCT = Randomized controlled trial

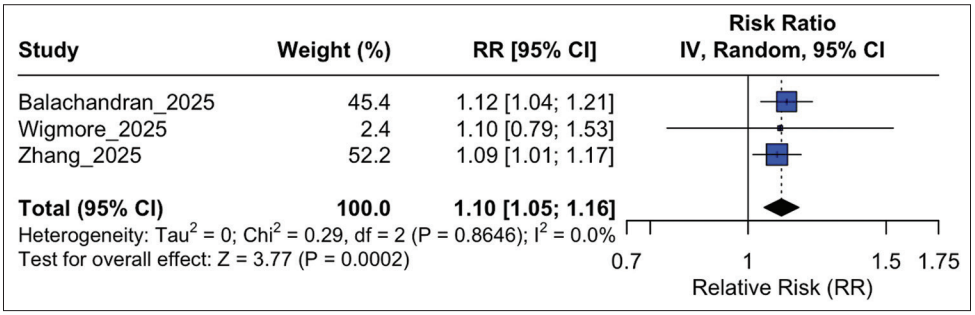

Figure 2: Primary meta-analysis of hyperoncotic albumin versus control on postoperative AKI. Forest plot of the association between albumin administration and any-stage acute kidney injury after adult cardiac surgery. Risk ratios are pooled with a random-effects model; squares show individual studies, and the diamond, the overall effect with 95% confidence intervals. AKI = Acute kidney injury

Primary outcome: Any-stage acute kidney injury

Three studies reported total AKI incidence within 7 days. In pooled analysis, 20% albumin was associated with a significant increase in AKI compared with crystalloid or 4% albumin (pooled RR = 1.10; 95% confidence interval [CI] 1.05–1.16; $P < 0.001$) with minimal heterogeneity (I^2 =0%) [Figure 2].[34] The prediction interval ranged from 0.99 to 1.23 [eFigure 1], implying

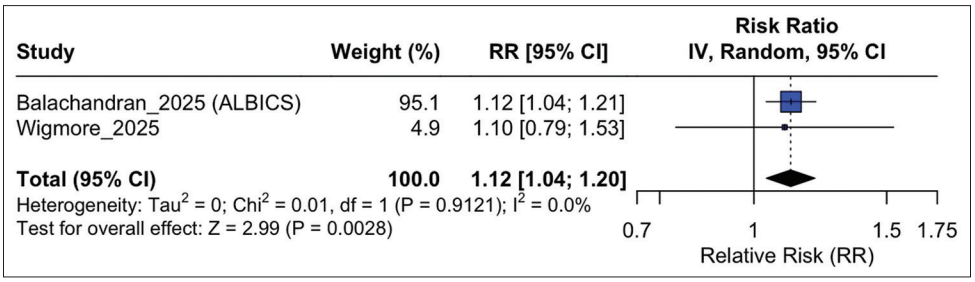

Figure 3: Trial-only synthesis (RCTs) for AKI. Forest plot of randomized controlled trials evaluating postoperative hyperoncotic albumin versus control for any-stage acute kidney injury after adult cardiac surgery, used to test the robustness of the primary meta-analytic result to study design. AKI = Acute kidney injury, RCT = Randomized controlled trial

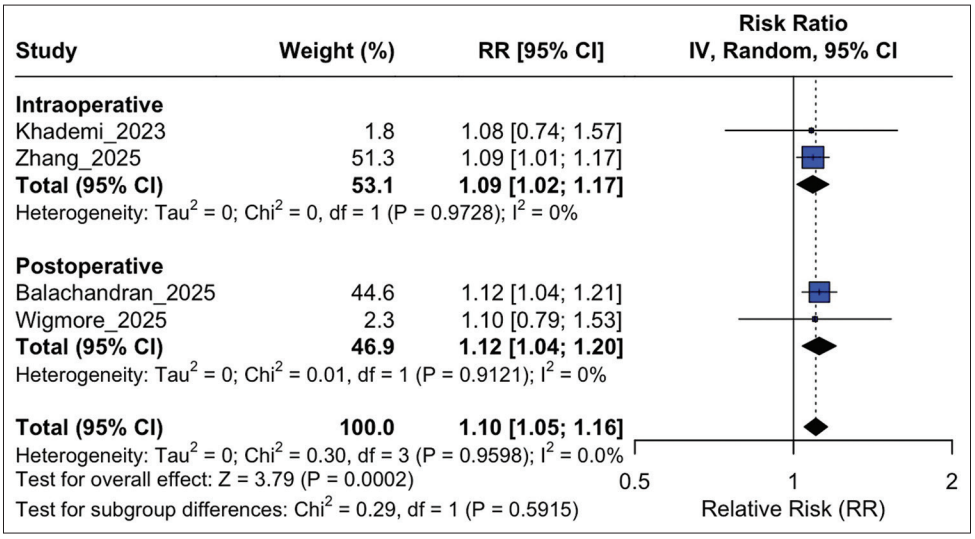

Figure 4: Timing analyses: Intraoperative versus postoperative albumin. Subgroup forest plot comparing intraoperative versus postoperative albumin administration for any-stage acute kidney injury, and meta-regression bubble plot exploring the association between timing of albumin exposure and log risk ratio of AKI. AKI = Acute kidney injury

the effect could be null in some settings but typically increases AKI risk. Restricting the analysis to the two RCTs yielded a similar estimate (RR = 1.12; 95% CI 1.04–1.20) [Figure 3],[34,35] confirming robustness. Both trials individually demonstrated higher AKI incidence in the albumin group; in ALBICS-AKI, adjusted RR for AKI was 1.12 (P = 0.003), and in HAS FLAIR II, the effect was not significant but directionally similar.[34,35] The large cohort study reported an adjusted odds ratio of 1.38 for AKI among patients with preoperative albumin >40 g/L.[36]

Subgroup analysis

Timing

Two studies administered albumin during surgery, and two administered it postoperatively. The pooled RR for intraoperative albumin was 1.09 (95% CI 1.02–1.17), and for postoperative albumin was 1.12 (95% CI 1.04–1.20) [Figure 4]. Mixed-effects meta-regression showed no significant interaction (P = 0.59). Thus, the deleterious effect of albumin on AKI did not differ materially with timing, indicating a general effect of 20% albumin.

Acute kidney injury severity

Across all included studies, Stage 1 AKI could be isolated and was analyzed as a prespecified secondary outcome. Albumin use increased the incidence of Stage 1 AKI (RR ≈ 1.11; 95% CI 1.03–1.20), similar in magnitude to the overall AKI result [eFigure 2]. Data on severe AKI and renal replacement therapy (RRT) were sparse and infrequently reported, and event numbers were low; available study-level data are summarized in Supplementary eTable 3.

Multiplicity control (false discovery rate)

To account for multiplicity across prespecified secondary comparisons, we applied the Benjamini–Hochberg FDR procedure. After FDR correction, the RCT-only meta-analysis and the analysis restricted to Stage 1 AKI remained statistically significant (both $q < 0.05$), whereas the timing subgroup interaction (intraoperative vs. postoperative) remained non-significant ($q > 0.10$) [eFigure 3]. These adjustments did not alter the direction or interpretation

Table 2: Risk of bias assessment

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Balachandran 2025	−	+	+	+	−	−
Wigmore 2025	+	+	−	+	−	−

Domains: D1: Bias arising from the randomized process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Biad in selection of the reported result.
Judgement: − Some concerns, + Low

Study	Risk of bias domains							
	D1	D2	D3	D4	D5	D6	D7	Overall
Khademi 2023	X	X	+	+	−	+	+	X
Zhang 2025	−	+	+	−	+	+	−	−

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.
Judgement: X Serious, − Moderate, + Low

of any secondary comparison. Full FDR-adjusted values are provided in the Supplement [eTable 4].[32] We did not formally assess small-study effects with funnel plots or Egger's test because fewer than 10 studies contributed to each synthesis.

Trial sequential analysis

TSA indicated that the cumulative information size of the RCTs (n = 1063) did not cross the harm or benefit boundaries [eFigure 4]. The RIS for detecting a 20% relative increase in AKI was ~1914 patients. The Z-curve of the RCTs approached but did not reach the harm boundary, indicating a potential signal but requiring more data to confirm or refute the effect. No futility boundaries were crossed. The overall certainty is limited by the small number of trials and the fact that the required information size was not met; thus, conclusions should be interpreted with caution.

DISCUSSION

Our systematic review and meta-analysis found that perioperative use of hyperoncotic (20%–25%) albumin is associated with a small but statistically significant increase in postoperative AKI compared with crystalloid-based care. The largest trial, ALBICS, reported higher AKI rates with albumin versus usual care; although the primary unadjusted analysis was not significant, adjusted models showed a modest but statistically significant increase.[34] In the ICU, bolus 20% albumin likewise failed to reduce AKI compared with crystalloids (HAS FLAIR II).[35] Collectively, randomized evidence does not support albumin for AKI prevention in on-pump CS.

In prespecified timing analyses, effect estimates were directionally consistent. If hyperoncotic albumin were renoprotective, a signal should be visible either during CPB (via the prime or intraoperative dosing) or within the first 24 h after surgery. In this review, neither intraoperative nor postoperative albumin reduced AKI incidence compared with control strategies. However, these analyses were based on a few studies and should be considered exploratory rather than definitive. When we restricted the analysis to Stage 1 AKI, the risk remained higher with albumin, which argues against the idea that albumin simply prevents small, clinically unimportant creatinine rises.

The most likely explanation is that theoretical benefits from higher oncotic pressure are offset by opposing mechanisms. Higher intravascular oncotic pressure may reduce transglomerular filtration pressure,[14] and delivery of a high protein load to the renal tubules may cause tubular injury.[15] Under these conditions, a net renoprotective effect is unlikely. Exploratory "trajectory"-based approaches to AKI risk remain hypothesis-generating and, so far, have not translated into fewer postoperative AKI events.[22] Changing the timing of hyperoncotic albumin alone is therefore unlikely to restore efficacy. Instead, effort is better directed toward guideline-concordant fluid strategies, such as balanced crystalloid-based resuscitation, avoidance of synthetic starches, and goal-directed hemodynamic management, and toward testing mechanism-driven renoprotective targets, including optimization of renal perfusion pressure and venous congestion, avoidance of nephrotoxins, and implementation of KDIGO-style AKI-prevention bundles.[1,9,22]

Confounding by indication is a key concern, particularly in the observational cohorts. In clinical practice, hyperoncotic albumin is often administered in response to hemodynamic instability, vasoplegia, capillary leak, or perceived risk of renal hypoperfusion—factors that are themselves strongly associated with postoperative AKI. In addition, differences in baseline kidney function, comorbidity burden (e.g., diabetes mellitus and hypertension), and procedural complexity (e.g., combined procedures and longer CPB duration) may influence both albumin

exposure and AKI risk. Accordingly, although we applied random-effects models and prespecified secondary analyses, residual confounding cannot be excluded, and observational findings should be interpreted as supportive and hypothesis-generating rather than definitive. Baseline characteristics may also explain part of the observed heterogeneity. Preoperative hypoalbuminemia can reflect systemic inflammation, capillary leak, malnutrition, or greater illness severity, all of which are independently associated with AKI risk and may increase the likelihood of receiving albumin. Likewise, lower baseline eGFR indicates reduced renal reserve and may amplify susceptibility to perioperative renal insults. Although Table 1 summarizes baseline albumin and kidney function where available, inconsistent reporting limited our ability to formally identify subgroups that might experience differential benefit or harm. These factors should be prespecified and consistently reported in future trials.

Baseline renal dysfunction is a clinically plausible effect modifier because reduced renal reserve may increase susceptibility to perioperative renal insults. However, the current evidence base does not allow robust inference in patients with pre-existing kidney dysfunction, as baseline eGFR (and chronic kidney disease (CKD) staging) was not consistently reported, and outcomes were rarely stratified by kidney function. Consequently, our findings should not be interpreted as establishing the safety of hyperoncotic albumin in patients with impaired baseline renal function, and future trials should prespecify eGFR strata and report AKI outcomes accordingly.

From a resource perspective, routine 20% albumin is difficult to justify. Albumin is a plasma-derived product; its manufacture requires donor recruitment, collection, fractionation, and strict viral inactivation and quality control. These steps are labor- and resource-exhaustive. As a result, albumin is substantially more expensive than crystalloids and is vulnerable to supply constraints. However, acquisition costs and availability vary across healthcare systems and over time, and we did not perform a formal cost-effectiveness analysis; therefore, our conclusions should be interpreted primarily through the balance of clinical benefit and harm rather than economic considerations alone. The 2024 international guideline, endorsed by the JSA, issues a conditional recommendation against albumin for CPB priming or routine volume expansion in adult CS, citing the absence of clinical benefit and higher cost.[20] Our findings are consistent with this position and support a crystalloid-first strategy,[9] reserving albumin for specific, high-yield indications rather than universal prophylaxis.

Our findings primarily address routine prophylactic strategies using 20%–25% albumin and should not be extrapolated to all albumin use scenarios. It remains possible that albumin may have a role in selected patients when administered using protocolized, trigger-based approaches (e.g., objective hemodynamic targets, markers of fluid responsiveness) and potentially at lower doses or different concentrations. Evaluating dose–response relationships and indication-specific protocols may help clarify whether albumin can be used without increasing AKI risk in carefully selected populations.

This study has several limitations. First, only two randomized datasets and two observational cohorts were eligible, limiting precision despite consistent point estimates. Second, albumin dose, timing, and co-administered fluids varied, leaving residual clinical heterogeneity and precluding a dose-response assessment. Third, observational analyses remain susceptible to confounding by indication despite adjustment, and the clinical triggers for albumin administration (for example, hypotension, vasoplegia, or presumed capillary leak) were not consistently reported. Fourth, to include all datasets, we pooled Stage 1 AKI as a secondary outcome, whereas data for severe AKI and dialysis were sparse and not meta-analyzed, so effects on harder renal endpoints remain uncertain. Importantly, clinically consequential endpoints such as severe AKI and RRT were infrequently and inconsistently reported across studies (definitions and time windows varied) [eTable 3]. Any-stage AKI is driven largely by stage 1 events, which may be transient and do not necessarily translate into persistent renal dysfunction or patient-centered outcomes. Therefore, the current evidence base is insufficient to determine whether hyperoncotic albumin influences severe AKI, RRT, or renal recovery, and any quantitative pooling based on sparse events would be unstable and potentially misleading. Fifth, outcome definitions (KDIGO vs. AKIN/RIFLE[24,25]) and the use of study-level rather than individual-patient data limited our ability to examine effect modification by baseline serum albumin concentration, preoperative estimated GFR, volume status, or CPB duration. It therefore remains unclear whether specific phenotypes—for example, patients with severe hypoalbuminemia but preserved GFR—experience different effects of albumin. In addition, renal injury biomarkers (e.g., neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, or cystatin C) were not systematically assessed in the included studies. Therefore, subclinical tubular injury or early renal stress potentially related to hyperoncotic albumin could not be evaluated using biomarker-based endpoints. Furthermore, baseline kidney function metrics were incompletely reported,

which prevented formal exploration of effect modification by eGFR using meta-regression and limited subgroup inference in patients with pre-existing renal dysfunction. Finally, comparator regimens ranged from crystalloid-only to crystalloids with occasional iso-oncotic (4%–5%) albumin, potentially diluting between-group differences.

TSA showed that the cumulative randomized evidence did not reach the required information size and that the monitoring boundaries for benefit, harm, and futility were not crossed.[33] A large benefit is therefore unlikely, but a small effect—either beneficial or harmful—cannot be excluded. Future multicenter RCTs with adequate statistical power should compare clearly defined albumin strategies, such as iso-oncotic versus hyperoncotic albumin or a restrictive, trigger-based albumin protocol versus no albumin. Background care should be standardized and reflect current best practice, including balanced crystalloids, avoidance of synthetic colloids, and KDIGO-style AKI-prevention bundles, so that any incremental effect of albumin is interpretable. These trials should stratify or adjust for baseline serum albumin concentration, preoperative renal function (for example, estimated GFR), intraoperative hemodilution, and other key risk factors. They should also prespecify patient-centered renal endpoints, including KDIGO AKI stages, need for RRT, and longer-term kidney function. Until such data emerge, routine hyperoncotic albumin for AKI prophylaxis in adult on-pump CS should be avoided. Renal-protective care should instead focus on early identification and optimization of high-risk patients, judicious use of balanced crystalloids, avoidance of fluid overload and venous congestion, minimization of nephrotoxins, and careful hemodynamic control during and after CPB. In this context, albumin can be reserved for situations in which its properties are most likely to be beneficial, such as marked hypoalbuminemia with ongoing third spacing or cases in which smaller-volume plasma expansion is needed to treat hypotension in patients at high risk of pulmonary edema. These selective indications are more consistent with current guideline recommendations than blanket use for AKI prophylaxis.

Future studies should prespecify and standardize (1) indications/triggers for albumin administration and dosing, (2) stratification by baseline eGFR/CKD status and preoperative serum albumin level, and (3) consistent outcome reporting, including severe AKI, RRT, renal recovery, and longer-term kidney function. Incorporating renal injury biomarkers alongside creatinine-based definitions may also improve mechanistic understanding. Pragmatic randomized trials embedded within contemporary perioperative AKI-prevention bundles would be particularly informative.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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eTable 1: Full search strategies (PubMed/Embase/CENTRAL)

Pubmed and Embase	Cochrane CENTRAL
((coronary artery bypass OR CABG OR heart valve replacement OR aortic surgery OR cardiac surgery) AND (cardiopulmonary bypass OR on-pump) AND (albumin OR "4% albumin" OR "5% albumin" OR "20% albumin" OR "25% albumin") AND ("acute kidney injury" OR AKI OR KDIGO) AND (randomized OR randomised OR trial OR retrospective OR cohort) AND (adult OR adults OR " ≥18 years"))	((CABG OR cardiac OR aortic OR valve) NEAR/3 (surg* OR bypass OR operation*)) AND ("4% albumin" OR "5% albumin" OR "20% albumin" OR "25% albumin") AND (kidney NEAR/3 injur* OR renal NEAR/2 fail* OR AKI) AND (randomi* OR trial*)

CABG = Coronary artery bypass graft, AKI = Acute kidney injury, KDIGO = Kidney disease: Improving Global Outcomes. Databases searched: PubMed, Embase (Ovid), Cochrane CENTRAL. Limits: Humans; Adults (≥ 18 y); RCTs = Randomized controlled trials; 1995/01/01 – 2025/07/17

eTable 2: Other study demographics and characteristics

Study ID	Country/ Center	Population	Operative data		Timing	Control	Concomitant Fluids	AKI Definition	AKI Rate (%)
			Bypass Time (Min)	Aortic Cross-Clamp Time (Min)					
Khademi_2023	Iran, single center	Elective on-pump CABG	69±22.5 67±24.3	38.20±12.2 38.56±15.1	During CPB prime	Balanced crystalloid prime	NR	AKIN stage 1, up to 72 h	9.5 8.3
Zhang_2025	China, 18 centers	Adult on-pump CABG/ valve/aortic surgery	118.4±41.9 119.8±43.6	86.1±34.3 87.1±36.0	Intraoperative (start of CPB)	No 20% albumin	Crystalloids±4% albumin	KDIGO to postop day 7	38.21 35.1
Balachandran_2025	Australia and Italy, 7 centers	High-risk adult on-pump surgery (eGFR <60 or combined operation)	137±49.6 138±56.4	105±40.5 106±45.6	ICU arrival ≤6 h start	Usual care	Center protocols (4% Alb allowed day 2)	KDIGO to postop day 7	48.9 43.4
Wigmore_2025	Australia and New Zealand, 6 centers	Adult post-cardiac surgery patients needing fluid bolus therapy in the ICU	NR NR	86.0±31.88 85.0±32.62	ICU admission period (≤24 h postop)	Crystalloid FBT (±4% Alb after 1 L)	As per protocol	KDIGO to postop day 7	24 22

CABG=Coronary artery bypass graft, AKI=Acute kidney injury, eGFR=Estimated Glomerular Filtration Rate, ICU=Intensive care unit, CPB=Cardiopulmonary bypass, AKIN=Acute Kidney Injury Network, KDIGO=Kidney disease: Improving Global Outcomes, postop=Postoperative, FBT=Fluid bolus therapy, NR = Not reported

eTable 3: Reporting of severe acute kidney injury and renal replacement therapy across included studies

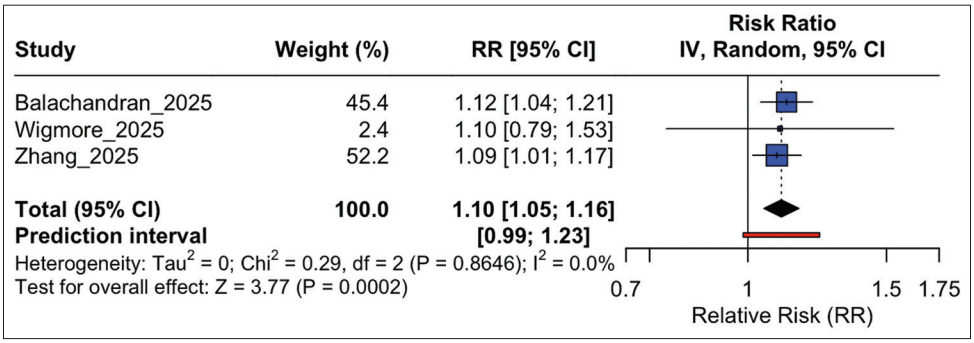
Study	Severe AKI Reported (How/When)	RRT Reported	RRT Events (Intervention)	RRT Events (Control)	Notes (Reporting/Extractability)
Khademi *et al*. 2023	AKI defined using AKIN and RIFLE criteria; AKIN stage 1 reported (48/260 vs. 42/246); renal failure not observed.	Reported (dialysis/RRT)	0/260	0/246	Abstract reports no renal failure and no dialysis requirement; stage 2/3 events not reported/absent.
Zhang *et al*. 2025	Moderate-to-severe CSA-AKI (KDIGO stage 2/3) analyzed (PSM/IPW); event counts not reported. CRRT reported as postoperative complication (stratified by baseline albumin).	Reported in the supplement (unmatched cohort) (CRRT)	24/2640 (0.9%)	112/24237 (0.5%)	CRRT counts derived by summing baseline-albumin strata in supplemental eTable 3. (prematching only)
Balachandran *et al*. 2025	Severe AKI reported as KDIGO stage II or III to Day 28 (28/307 vs. 28/304).	Yes (CRRT)	10/307 (3.3%)	7/304 (2.3%)	Values from ALBICS supplemental eTable 4 (Day 28 outcomes).
Wigmore *et al*. 2025	Severe AKI reported as KDIGO stage 2 or 3 within 7 days (15 [5%] vs. 14 [4%]).	Yes (kidney replacement therapy).	3/224 (1.3%)	3/228 (1.3%)	RRT data reported as kidney replacement therapy; denominators not extractable from PDF text layer (reported as *n* [%]).

RRT=Renal replacement therapy, AKI=Acute kidney injury, KDIGO=Kidney Disease: Improving Global Outcomes, AKIN=Acute Kidney Injury Network, RCT=Randomized controlled trial, CRRT=Continuous renal replacement therapy, NR=Not reported or not extractable from the published report for the present review, RIFLE = Risk, injury, failure, loss of kidney function, and End-stage kidney disease, CSA-AKI = Cardiac surgery-associated acute kidney injury, PSM = Propensity score matching, IPW = Inverse probability weighting, ALBICS = Albumin in cardiac surgery

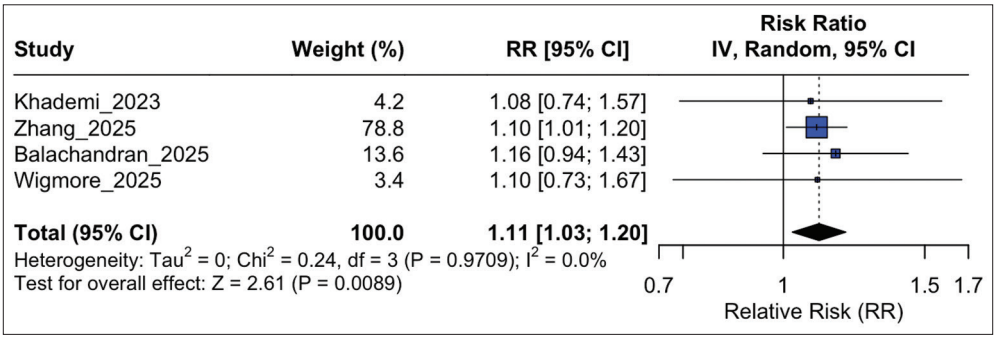
eTable 4: Multiplicity-adjusted results (false discovery rate)

Analysis	*P*	*q*
Only RCT	0.0028	0.0112
AKI only Stage 1	0.0089	0.0178
Subgroup differences	0.5915	0.5915
Meta-regression	0.5915	0.5915

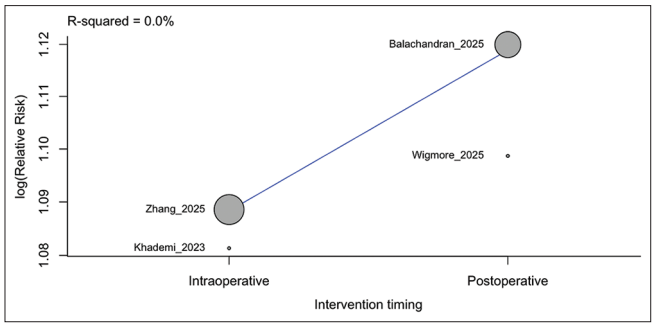
AKI=Acute kidney injury, RCT=Randomized controlled trial



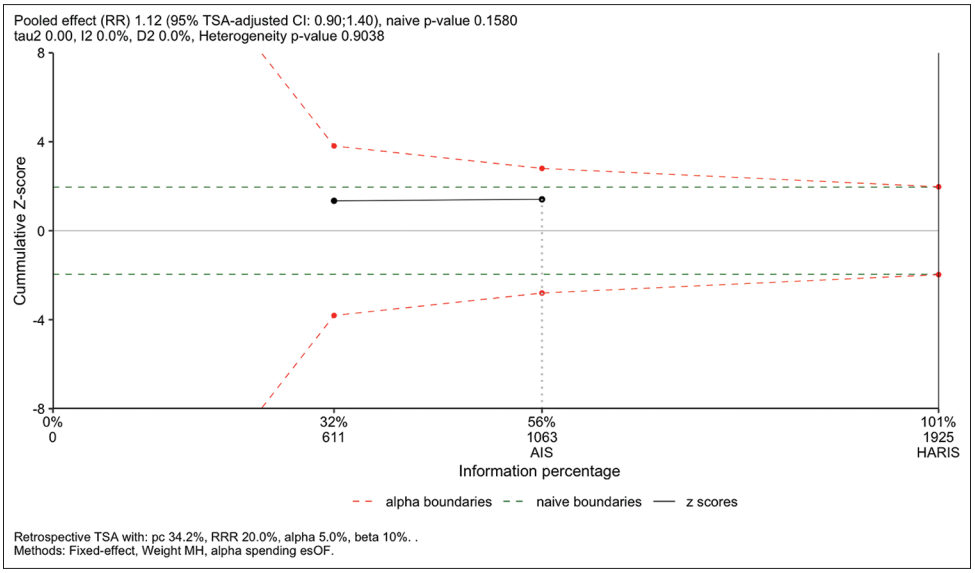
eFigure 1: Prediction interval. RR= risk ratio, CI= confidence interval, IV = inverse variance



eFigure 2: Detailed forest plot—Stage 1 AKI only. AKI = Acute kidney injury, RR= risk ratio, CI = confidence interval; IV = inverse variance



eFigure 3: Timing subgroup (intraoperative versus postoperative - meta-regression)



eFigure 4: Trial sequential analysis. RR= risk ratio, AIS= accrued information size, HARIS= heterogeneity-adjusted required information size, pc= proportion of events in the control group, RRR= relative risk reduction, MH= Mantel-Haenszel, esOF= O'Brien-Fleming