

Effect of Albumin Infusion on Renal Outcomes in Sepsis Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: Sepsis is a severe systemic inflammatory condition often complicated by acute kidney injury (AKI). Although albumin is widely applied for fluid resuscitation with theoretical renoprotective effects, its optimal administration and actual influence on renal function remain unclear. This study aimed to explore whether albumin infusion reduces the risk of renal injury in adult patients with sepsis. **Methods:** We systematically searched CENTRAL, Embase, and MEDLINE from database inception to May 20, 2026 to retrieve eligible randomized controlled trials (RCTs) comparing human albumin infusion with alternative fluid therapies in adult septic patients. The primary outcome was the incidence of AKI. Secondary outcomes included the requirement for renal replacement therapy (RRT), 90-day mortality, and pulmonary edema. Pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated via a random-effects model. **Results:** A total of nine RCTs involving 5003 participants were included. Compared with control fluid regimens, albumin infusion was not associated with a decreased risk of AKI (RR 1.04, 95% CI 0.95–1.13, $P = 0.41$). No significant intergroup differences were observed regarding RRT requirement (RR 1.06, 95% CI 0.94–1.20, $P = 0.34$) or 90-day mortality (RR 0.98, 95% CI 0.90–1.08, $P = 0.74$). Nevertheless, albumin infusion significantly elevated the risk of pulmonary edema (RR 2.38, 95% CI 1.28–4.42, $P = 0.006$). Subgroup analyses confirmed neutral renal effects of albumin regardless of albumin concentration (20% vs. 4–5%). **Conclusions:** Albumin infusion fails to lower AKI risk or improve survival outcomes among septic patients, whereas it significantly increases the risk of pulmonary edema. Routine albumin resuscitation cannot be recommended for sepsis treatment; individualized fluid management should be prioritized in clinical practice.

Keywords: Albumin; Acute Kidney Injury; Fluid Resuscitation; Meta-analysis; Pulmonary Edema; Renal Replacement Therapy; Sepsis.

1. Introduction

Patients with sepsis develop overwhelming systemic inflammation. This pathological state frequently induces extensive damage to the endothelial glycocalyx, leading to high mortality rates[1]. Acute kidney injury (AKI) represents one of the most common and devastating complications of sepsis, which substantially increases medical burden, prolongs hospital stay, and worsens long-term prognosis[2]. Prompt fluid resuscitation constitutes the core strategy for initial sepsis management[3], and albumin is frequently selected as a colloidal volume expander.

As a natural plasma colloid, albumin maintains plasma colloid osmotic pressure, suppresses inflammatory responses, and protects vascular endothelial barriers. Theoretically, albumin can sustain stable renal perfusion and reduce tissue edema, thereby exerting potential protective effects on kidney and lung tissues[4, 5].

Despite these theoretical advantages, the actual renal protective effect of albumin in septic patients remains controversial. Multiple landmark RCTs have evaluated albumin application in sepsis populations, yet these trials were primarily powered to assess overall mortality[6–8]. Renal outcomes were only reported as secondary endpoints with insufficient statistical power, generating inconsistent results across published studies.

To date, no comprehensive quantitative meta-analysis has specifically clarified the impact of albumin infusion on renal dysfunction risk in sepsis. To fill this critical research gap, we

performed a systematic review and meta-analysis of all relevant RCTs. With AKI incidence and pulmonary safety as core endpoints, this work aimed to quantify the renal risk associated with albumin administration and provide high-quality evidence to guide fluid resuscitation strategies in intensive care units.

2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[9]. The review protocol was prospectively registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (PROSPERO), registration number: CRD420251168196.

Search Strategy: Three electronic databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched from database inception to May 20, 2026. Search terms combined medical subject headings and free-text keywords related to albumin, sepsis, and septic shock, with validated RCT search filters applied.

Eligibility Criteria: Studies were included if they met all the following predefined criteria:

Population: Adult patients aged ≥ 18 years diagnosed with sepsis, severe sepsis, or septic shock;

Intervention: Intravenous human albumin administered for fluid resuscitation or volume expansion;

Comparator: Alternative fluid treatments (balanced

crystalloids, normal saline, or fluid regimens without albumin);

Outcomes: Original data reporting AKI incidence or severity, or the requirement for RRT;

Study design: Parallel-group randomized controlled trials.

Study Selection Process: Two independent reviewers screened all retrieved records sequentially. Duplicate literatures were removed first, followed by title and abstract screening to exclude irrelevant studies. Full-text articles of potentially eligible records were retrieved and assessed against the eligibility criteria. Any disagreements between the two reviewers were resolved via discussion with a third senior reviewer.

Data Extraction: Two investigators independently extracted standardized data using pre-designed electronic extraction forms. Extracted information covered first author, publication year, study country, enrolled population, sample size of albumin and control groups, albumin concentration, dosage and infusion protocols, control group interventions, and all predefined clinical outcomes. Discrepancies in extracted data were adjudicated by a third reviewer.

Outcome Definitions: The primary outcome was the incidence of new-onset AKI during follow-up. Secondary outcomes included the requirement for RRT, pulmonary edema, and all-cause 90-day mortality. Outcome definitions and follow-up durations strictly followed the criteria described in each original trial.

Risk of Bias Assessment: The revised Cochrane risk-of-bias tool (RoB 2) was applied to evaluate the methodological quality of all included RCTs[10]. Seven bias domains were assessed: (1) bias arising from random sequence generation; (2) bias due to allocation concealment; (3) bias due to deviations from intended interventions; (4) bias from incomplete outcome data; (5) bias in outcome measurement;

(6) bias from selective outcome reporting; (7) other potential sources of bias. Each trial was categorized as low risk, some concerns, or high risk of bias for each domain.

Evidence Certainty Evaluation: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to rate the certainty of evidence for all primary and secondary outcomes. Five evaluation domains were considered: risk of bias, study inconsistency, indirectness of evidence, statistical imprecision, and additional factors (publication bias, large treatment effects, plausible confounding factors, and dose-response gradients) [11]. Evidence certainty was classified as high, moderate, low, or very low.

Statistical Analysis: Meta-analyses were performed using the Mantel-Haenszel method to calculate pooled RRs and corresponding 95% CIs. A random-effects model was adopted for all pooled analyses to account for potential clinical heterogeneity across trials. Forest plots were generated to visualize pooled effect sizes. Cochran's Q test and the I^2 statistic were used to quantify inter-study heterogeneity. Substantial statistical heterogeneity was defined as $I^2 > 50\%$. Publication bias was assessed via visual inspection of funnel plots and Egger's regression test[12]. All statistical analyses were conducted using RevMan 5.4 and R software (version 4.5.1). A two-tailed p value < 0.05 was defined as the threshold for statistical significance.

Subgroup Analysis: Prespecified subgroup analysis was performed stratified by albumin concentration (20% hyperoncotic albumin vs. 4–5% iso-oncotic albumin) to test whether albumin concentration modified the association between albumin infusion and AKI risk.

3. Results

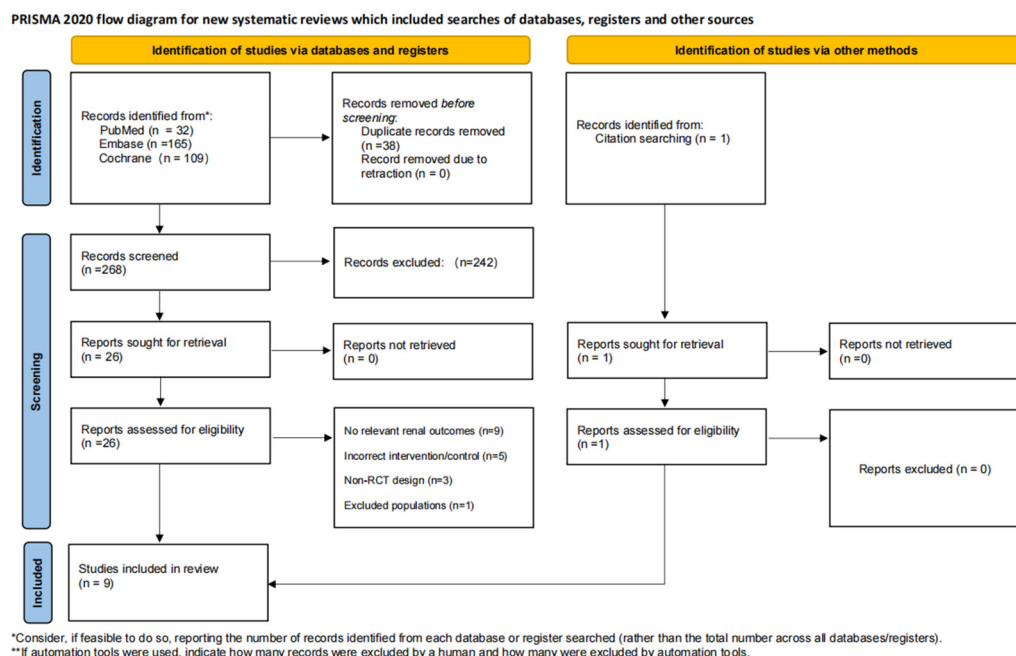


Figure 1. PRISMA 2020 flow diagram illustrating the complete literature search and study selection process

Study Selection: The full literature screening process is illustrated in Figure 1. Initially, 306 unique records were retrieved from PubMed (n = 32), Embase (n = 165), and CENTRAL (n = 109). After duplicate removal (n = 38), 268

records remained for title and abstract screening, among which 242 irrelevant records were excluded. A total of 26 full-text articles plus one additional citation from reference screening were retrieved for eligibility assessment. Eighteen

full-text articles were excluded for predefined reasons: nine without relevant renal outcomes, five with ineligible intervention or comparator regimens, three non-RCT designs, and one recruiting excluded populations. Ultimately, nine RCTs with 5003 total participants were included in the quantitative meta-analysis [13-21].

Baseline Characteristics of Included Trials: Baseline characteristics of all nine eligible RCTs are summarized in Table 1. Trials were published between 2011 and 2026, with sample sizes ranging from 100 to 1818 participants. Study sites covered Europe, Asia, South America, and Oceania. Enrolled populations included isolated septic shock, severe sepsis, general emergency department sepsis, and sepsis superimposed on liver cirrhosis. Intervention groups received 4%, 5%, or 20% albumin. Control groups mainly received balanced crystalloids, normal saline, or standard antibiotic supportive care without albumin. AKI diagnostic criteria varied across trials; five RCTs adopted the KDIGO definition, while others applied RIFLE or serum creatinine thresholds.

Risk of Bias Assessment: The overall risk of bias summary for all included RCTs is displayed in Figure 2. Six

trials were rated as low overall risk of bias, one trial had some concerns regarding bias, and two trials demonstrated high overall risk of bias. The primary source of bias was deviations from intended interventions, driven by open-label study designs without participant or clinician blinding. Bias related to randomization sequence generation, missing outcome data, outcome measurement, and selective reporting remained low across most trials.

GRADE approach: The certainty of evidence for each outcome was assessed using the GRADE approach (Table 2). Albumin administration did not significantly reduce the risk of acute kidney injury (AKI) (RR 1.04, 95% CI 0.95 to 1.13; moderate certainty), the requirement for renal replacement therapy (RRT) (RR 1.06, 95% CI 0.94 to 1.20; moderate certainty), or 90-day mortality (RR 0.98, 95% CI 0.90 to 1.08; moderate certainty). However, albumin was associated with a significantly increased risk of pulmonary edema (RR 2.38, 95% CI 1.28 to 4.42; low certainty), with the absolute risk rising from 39 per 1,000 in the control group to 93 per 1,000 in the albumin group.



Figure 2. Summary plot of Cochrane RoB 2 risk-of-bias evaluation for all included RCTs

Primary Outcome: Incidence of AKI: All nine RCTs enrolling 5003 patients reported AKI incidence data. Pooled analysis demonstrated no significant difference in AKI risk between albumin infusion and control fluid therapy (RR 1.04,

95% CI 0.95–1.13, P = 0.41). No statistically significant inter-study heterogeneity was detected (I² = 0%, P = 0.66). The corresponding forest plot is shown in Figure 3.

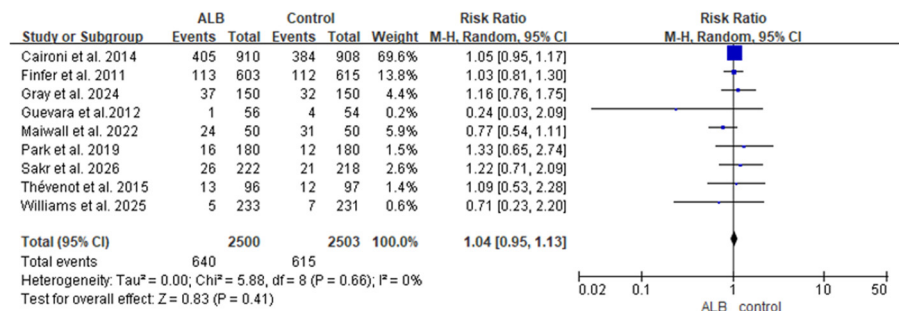


Figure 3. Forest plot for the primary outcome: pooled risk ratio of incident AKI comparing albumin infusion versus control fluid therapy

Table 1. Baseline clinical characteristics of included randomized controlled trials

First author (year)	Country	Population	Sample size (Alb/Control)	Albumin concentration	Control group	Outcomes	AKI definition
Sakr 2026	Germany	Septic shock	222 / 218	20%	Standard Care	28-day mortality; 90-day mortality; New AKI (KDIGO); Requirement for RRT; SOFA score evolution	KDIGO criteria
Williams 2025	Australia	Sepsis in ED	233 / 231	20%	Crystalloid	SBP at 24 hours; SBP at 6h; Fluid/vasopressor requirements; Organ dysfunction (AKI); Mortality	KDIGO criteria
Gray 2024	UK	Sepsis in ED	150 / 150	5%	Balanced crystalloid	Recruitment rate and 30-day mortality; AKI incidence; RRT requirement; Organ support-free days; ICU/hospital stay	KDIGO criteria
Maiwall 2022	India	Cirrhosis + Sepsis	50 / 50	20%	Plasmalyte	Reversal of sepsis-induced hypotension; 28-day survival; AKI incidence; Requirement for RRT; Pulmonary complications	KDIGO criteria
Park 2019	Brazil	Sepsis in cancer patients	180 / 180	4%	Lactated Ringer's	7-day survival; 28-day survival; AKI incidence (at 48h/7d); RRT requirement; Vasopressor-free days	KDIGO criteria

Table 1. (continued)

First author (year)	Country	Population	Sample size (Alb/Control)	Albumin concentration	Control group	Outcomes	AKI definition
Caironi 2014	Italy	Severe sepsis / septic shock	910 / 908	20%	Crystalloids	28-day mortality; 90-day mortality; New organ failures (including renal); RRT requirement; ICU/hospital stay	RRT requirement
Guevara 2012	Spain	Cirrhosis with non-SBP bacterial infections	56 / 54	20%	Antibiotics only (no fluid)	3-month survival; Renal function; Circulatory function	Serum creatinine >1.5 mg/dl or >50% increase to >1.5 mg/dl
Thévenot 2015	France	Cirrhosis with non-SBP infection	96 / 97	20%	Antibiotics only	3-month survival; AKI incidence (at 7 days); Requirement for RRT; Circulatory/Renal function improvement	Serum creatinine >1.5 mg/dl
Finfer 2011	Australia / New Zealand	Severe sepsis in ICU	603 / 615	4%	0.9% Saline	28-day mortality; 90-day mortality; New organ failure (including AKI); Duration of ICU/hospital stay; RRT requirement	RIFLE criteria

Abbreviations: Alb, albumin; SBP, spontaneous bacterial peritonitis; ED, emergency department; AKI, acute kidney injury; RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.

Note: Sample size is presented as albumin group / control group

Subgroup Analysis Stratified by Albumin Concentration: Subgroup analysis stratified by albumin concentration yielded consistent neutral renal effects across both subgroups. For trials using 20% albumin, pooled RR for AKI was 0.94 (95% CI 0.81–1.09, $P = 0.39$, $I^2 = 0\%$). For

trials using 4–5% albumin, pooled RR for AKI was 1.08 (95% CI 0.89–1.32, $P = 0.42$, $I^2 = 0\%$). The test for subgroup difference showed no significant modification of treatment effect by albumin concentration ($P = 0.25$, $I^2 = 25.5\%$). The stratified forest plot is presented in Figure 4.

Table 2. GRADE evidence profile and summary of findings for each outcome

Outcomes	Risk with Control	Risk with Albumin	Relative effect (95% CI)	NO of participants (studies)	Certainty of the evidence (GRADE)	Comments
Incidence of AKI	246 per 1,000	256 per 1,000 (233 to 278)	RR 1.04 (0.95 to 1.13)	5,003 (9 RCTs)	⊕⊕⊕○ Moderate ^a	Albumin does not significantly reduce the risk of AKI.
Requirement for RRT	161 per 1,000	171 per 1,000 (151 to 193)	RR 1.06 (0.94 to 1.20)	4,700 (7 RCTs)	⊕⊕⊕○ Moderate ^a	Albumin does not significantly reduce the need for RRT.
90-day Mortality	374 per 1,000	367 per 1,000 (337 to 404)	RR 0.98 (0.90 to 1.08)	2,741 (5 RCTs)	⊕⊕⊕○ Moderate ^a	Albumin does not significantly improve 90-day survival.

Table 2. (continued)

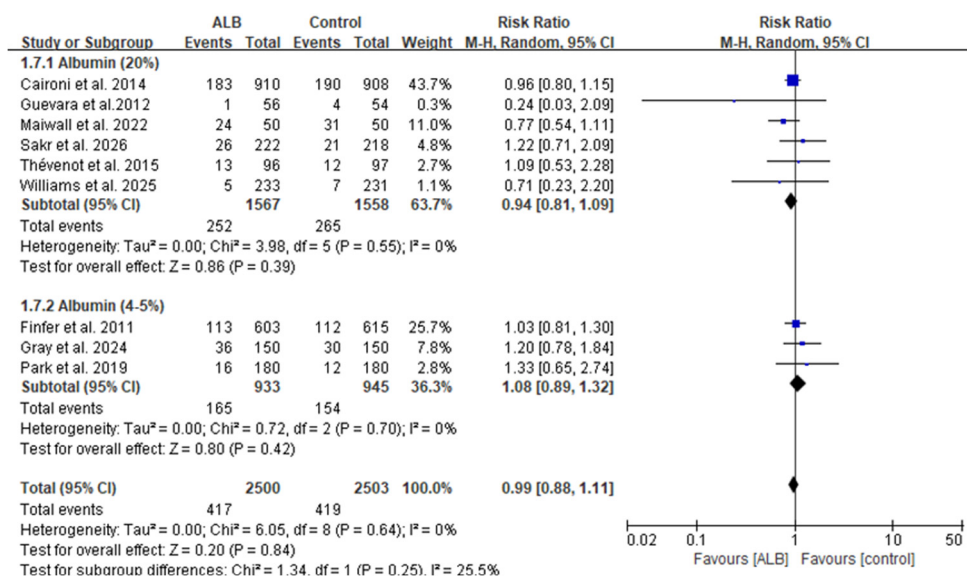
Outcomes	Risk with Control	Risk with Albumin	Relative effect (95% CI)	NO of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pulmonary Edema	39 per 1,000	93 per 1,000 (50 to 172)	RR 2.38 (1.28 to 4.42)	656 (4 RCTs)	⊕⊕○○ Low ^{b, c}	Albumin is associated with a significantly increased risk of pulmonary edema.

GRADE Working Group grades of evidence High certainty (⊕⊕⊕⊕): We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty (⊕⊕⊕○): We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty (⊕⊕○○): Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty (⊕○○○): We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Figure 4.** Subgroup forest plot for AKI risk stratified by albumin concentration (20% vs. 4–5%).

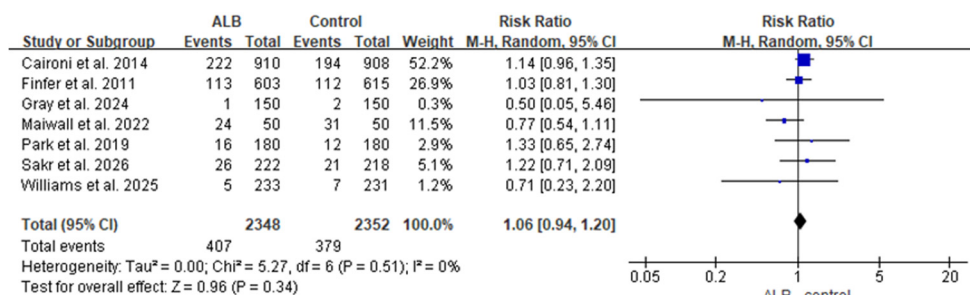


Figure 5. Forest plot for secondary outcome: pooled RR of RRT requirement (albumin vs. control fluids)

Secondary Outcomes: Requirement for Renal Replacement Therapy.

Seven trials reported RRT utilization data. No significant difference in RRT requirement was observed between albumin and control groups (RR 1.06, 95% CI 0.94–1.20, $P = 0.34$, $I^2 = 0\%$). Forest plot is shown in Figure 5.

90-Day All-Cause Mortality: Five trials reported 90-day mortality endpoints. Pooled analysis indicated no survival benefit associated with albumin infusion (RR 0.98, 95% CI 0.90–1.08, $P = 0.74$, $I^2 = 0\%$). Forest plot is shown in Figure 6.

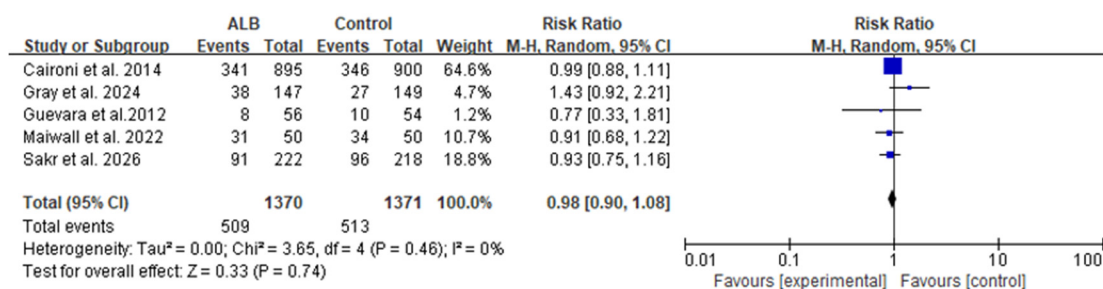


Figure 6. Forest plot for secondary outcome: pooled RR of 90-day all-cause mortality (albumin vs. control fluids)

Risk of Pulmonary Edema: Four trials reported pulmonary edema events. Albumin infusion was associated with a statistically significant increase in pulmonary edema

risk (RR 2.38, 95% CI 1.28–4.42, $P = 0.006$, $I^2 = 0\%$). Forest plot is shown in Figure 7.

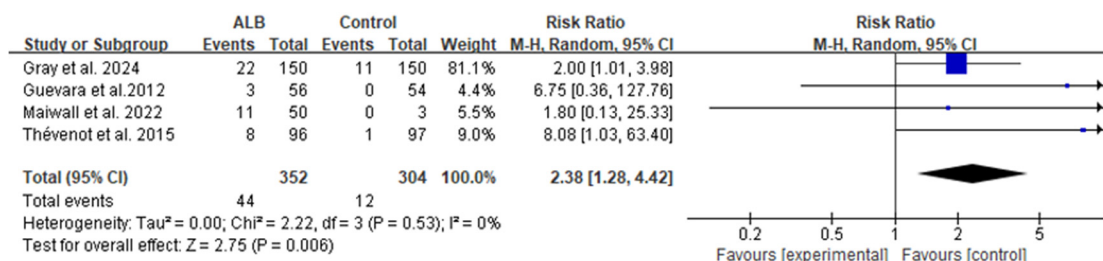


Figure 7. Forest plot for secondary outcome: pooled RR of pulmonary edema (albumin vs. control fluids)

4. Discussion

This systematic review and meta-analysis of nine RCTs comprehensively evaluated renal safety and clinical efficacy of albumin volume resuscitation in critically ill septic patients. The core pooled results demonstrated that albumin infusion did not reduce AKI incidence or the need for RRT relative to other fluid regimens. Furthermore, albumin administration failed to improve 90-day survival. Notably, albumin significantly increased the risk of pulmonary edema, challenging the universal clinical practice of routine albumin infusion for renoprotection in sepsis.

The contradiction between theoretical renoprotective properties of albumin and neutral renal clinical outcomes can be explained by sepsis-induced capillary leak syndrome. The endothelial glycocalyx maintains normal vascular barrier integrity [22]. Severe inflammatory injury in sepsis degrades the glycocalyx layer, disrupting microvascular barrier function and inducing pathological hyperpermeability [23]. Exogenously administered albumin rapidly extravasates from

intravascular spaces into interstitial tissue [25,26], driving interstitial fluid accumulation and renal interstitial edema [27]. Elevated intrarenal interstitial pressure reduces renal perfusion reserve, impairs microcirculatory venous drainage, and ultimately triggers hypoxic tubular epithelial injury and AKI [28,29].

Subgroup analysis stratified by albumin concentration confirmed consistent neutral renal effects for both hyperoncotic (20%) and iso-oncotic (4–5%) albumin preparations, with no significant subgroup interaction ($P = 0.25$). This finding indicates that altering colloid osmotic pressure via different albumin formulations cannot reverse the capillary leak-mediated renal injury in sepsis.

The elevated risk of pulmonary edema (RR = 2.38, $P = 0.006$) represents a critical safety signal with consistent pathophysiological mechanisms. In severe inflammatory states, degraded endothelial barriers destroy normal Starling fluid exchange balance [26]. Hyperoncotic albumin initially shifts interstitial fluid into the circulation, abruptly elevating pulmonary capillary hydrostatic pressure [30,31]. Due to

disrupted pulmonary vascular permeability, albumin and accumulated fluid rapidly leak into lung interstitium, reversing transvascular osmotic gradients and continuously drawing fluid into alveolar tissue, exceeding pulmonary lymphatic drainage capacity [32,33]. Combined elevated hydrostatic and interstitial oncotic pressure disrupts alveolar gas exchange and increases pulmonary edema risk.

Statistical heterogeneity for the primary outcome was zero ($I^2 = 0\%$), despite clinical diversity across trial populations (general sepsis, cirrhosis-associated sepsis, emergency department and ICU cohorts). This homogeneity reflects uniform neutral net renal effects of albumin across all clinical subgroups, rather than identical trial design. Two large landmark RCTs (Caironi 2014; Finfer 2011) carried dominant statistical weight in the random-effects model, compressing pooled variance and eliminating minor between-trial fluctuations in smaller studies [34,35].

No significant 90-day mortality difference was detected between albumin and control groups, consistent with a recent updated systematic review [6]. Discrepancies with earlier meta-analyses reporting survival benefits [7,8] are attributable to heterogeneous enrolled populations, variable albumin dosage protocols, and different comparator fluid regimens. Survival advantages reported in older analyses were limited to highly specific subgroups receiving high-dose 20% albumin (> 0.5 g/kg daily).

Heterogeneous AKI diagnostic criteria across trials (KDIGO, RIFLE, isolated serum creatinine thresholds) may introduce classification bias in outcome ascertainment. Clinical heterogeneity existed across study populations, comparator fluid types, and albumin concentration regimens, which limits broad generalizability of findings to every critically ill subgroup. Pooled effect estimates were largely driven by two large mega-trials; multiple open-label trial designs introduced potential performance bias. Pathophysiological explanations regarding endothelial glycocalyx degradation and capillary leak are extrapolated from preclinical basic research and cannot be directly validated by meta-analyzed clinical endpoint data.

5. Clinical Implications

Routine albumin infusion cannot be recommended as first-line resuscitation fluid to prevent AKI in sepsis, given its neutral renal impact, lack of survival benefit, and elevated risk of pulmonary edema. Clinical fluid management should shift from standardized universal protocols to individualized strategies.

When albumin is clinically necessary for volume expansion, clinicians must implement rigorous dynamic monitoring of respiratory function, cumulative fluid balance, and tissue perfusion markers to mitigate fluid overload and pulmonary complications.

6. Conclusion

Based on all available RCT evidence, routine albumin infusion does not confer renal protective effects for critically ill patients with sepsis or cirrhosis, while significantly increasing pulmonary edema risk. Uniform albumin-based fluid resuscitation protocols are not supported by current data. Individualized fluid therapy is required to balance hemodynamic volume demands against each patient's risk of capillary leak and respiratory deterioration. Future research should focus on phenotype-specific RCTs to identify

subgroups that may derive targeted benefit from albumin, and validate dynamic monitoring tools to prevent fluid overload complications.

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