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Efficacy and Safety of Acute Normovolemic Hemodilution in Adult Cardiac Surgery: A Systematic Review and Meta-Analysis of Latest Evidence

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Abstract

Acute normovolemic hemodilution (ANH) is a blood-conservation technique used during cardiac surgery to reduce allogeneic blood transfusion requirements and perioperative blood loss. This systematic review and meta-analysis (SRMA) aimed to evaluate the efficacy and safety of ANH in adults undergoing cardiac surgery. PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library were searched for randomized controlled trials (RCTs) and comparative observational studies published between January 2005 and August 2026. Meta-analyses were performed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, London, United Kingdom) with random-effects models. Continuous outcomes were pooled as mean differences (MDs), whereas dichotomous outcomes were pooled as risk ratios (RRs); both were reported with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$, and heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Fourteen studies were included. ANH was associated with reduced postoperative chest tube drainage across eight studies (MD, −66.74 mL; 95% CI, −121.45 to −12.02; $P = 0.02$; $I^2 = 93\%$). Across seven studies, ANH was associated with a shorter hospital stay (MD, −0.75 days; 95% CI, −1.00 to −0.51; $P < 0.00001$; $I^2 = 92\%$). The pooled analysis of perioperative RBC utilization showed a reduction in the number of RBC units transfused across 10 studies (MD, −0.34 units; 95% CI, −0.61 to −0.07; $P = 0.01$; $I^2 = 85\%$). ANH was not associated with a statistically significant reduction in cardiac surgery-associated acute kidney injury (CSA-AKI) (RR, 0.84; 95% CI, 0.67-1.06; $P = 0.15$; $I^2 = 0\%$). No statistically significant differences were reported for platelet or fresh frozen plasma (FFP) transfusion. Substantial heterogeneity was observed for chest tube drainage, hospital length of stay, and RBC utilization. ANH may reduce postoperative chest tube drainage, hospital length of stay, and perioperative RBC requirements in adults undergoing cardiac surgery. However, substantial heterogeneity across several outcomes and the absence of statistically significant differences in CSA-AKI and other transfusion outcomes warrant cautious interpretation. Further well-designed studies are needed to clarify its benefits across different cardiac surgical populations.

Categories: Internal Medicine, Cardiac/Thoracic/Vascular Surgery, Anesthesiology
Keywords: acute kidney injury, acute normovolemic hemodilution, blood conservation, cardiac surgery, chest tube drainage, hospital length of stay, red blood cell transfusion

Introduction And Background

Cardiac surgery is frequently complicated by perioperative anemia and blood loss, particularly during procedures requiring cardiopulmonary bypass (CPB). CPB temporarily takes over the functions of the heart and lungs during surgery. A preset volume of the patient's whole blood is drawn before surgery and replaced with crystalloid or colloid to maintain normovolemia during acute normovolemic hemodilution (ANH), a blood-conservation procedure. Following CPB, the extracted autologous blood is reinfused, limiting the patient's exposure to allogeneic blood products while preserving their own red blood cells (RBCs) and coagulation factors [1,2].

Perioperative anemia and transfusion in cardiac surgery are still a significant burden. Hemodilution and reduced coagulation factor levels after cardiac surgery, due to CPB circuit priming, cardioplegia (the administration of a solution to temporarily stop the heart during surgery), and intraoperative fluid administration, are also associated with increased bleeding and transfusion requirements. Contemporary

evidence suggests that anemia is common in patients presenting for cardiac surgery [3,2]. Although allogeneic transfusion can be lifesaving, it carries potential risks, including transfusion reactions, transfusion-related acute lung injury, circulatory overload, and immunomodulatory effects. Furthermore, transfusion increases healthcare costs through blood collection, processing, storage, compatibility testing, and administration. Reducing avoidable allogeneic transfusions is therefore an important component of patient blood management (PBM) [4,5].

Conventional management has therefore included multimodal PBM strategies such as preoperative anemia optimization, restrictive transfusion strategies, antifibrinolytic therapy, cell salvage, meticulous surgical hemostasis, and strategies to minimize hemodilution associated with CPB. Despite these measures, allogeneic transfusion remains common, highlighting the need for additional strategies [2,4,5].

Previous randomized trials and meta-analyses have suggested that ANH may reduce perioperative RBC transfusion requirements. However, the magnitude of benefit has varied according to patient characteristics, surgical procedures, and the volume of blood withdrawn [1,2,6]. Previous studies have examined different aspects of perioperative transfusion and blood conservation in cardiac surgery. Welsby et al. [7] evaluated pathogen-reduced RBCs in cardiac surgical patients, providing evidence relevant to transfusion-related outcomes, although their study did not directly investigate ANH. Bugo et al. [8] examined the robustness of evidence from randomized trials of ANH, highlighting the importance of critically evaluating the available evidence.

Despite several previous systematic reviews and meta-analyses, uncertainty remains regarding the contemporary effectiveness and safety of ANH in cardiac surgery. Differences in study populations, surgical procedures, ANH protocols, transfusion thresholds, and outcome definitions may contribute to the inconsistent findings across studies. Furthermore, the balance between potential reductions in allogeneic blood product exposure and clinically important postoperative complications, particularly CSA-AKI, requires further evaluation. An updated synthesis incorporating the most recent eligible evidence is therefore warranted to reassess the effect of ANH on transfusion requirements and postoperative outcomes. Unlike earlier reviews, the present study evaluates both transfusion-related outcomes, including the use of different allogeneic blood components, and clinically relevant postoperative complications using the available randomized and eligible observational evidence. This broader assessment aims to provide an updated evaluation of the benefits and potential risks of ANH and clarify its role in contemporary cardiac surgical PBM.

Review

Study design and reporting

This systematic review and meta-analysis (SRMA) aimed to assess the effectiveness and safety of ANH in patients undergoing cardiac surgery. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (CRD420261501187) guidelines [9].

Literature search strategy

We conducted a systematic literature search in PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library to identify studies evaluating ANH in patients undergoing cardiac surgery. The search covered the period from January 2005 to August 2026. Database-specific search strategies combined relevant Medical Subject Headings (MeSH), Emtree terms, and free-text keywords related to ANH, including “acute normovolemic hemodilution,” “acute normovolaemic haemodilution,” “normovolemic hemodilution,” and “isovolemic hemodilution,” with terms related to cardiac surgery, heart surgery, CPB, coronary artery bypass grafting, and valve surgery. Boolean operators (AND and OR) were used to combine search terms, and the strategies were adapted to the syntax and indexing requirements of each database. The reference lists of relevant studies and previous systematic reviews were also examined to identify additional eligible publications. All retrieved records were screened according to the prespecified eligibility criteria, and potentially relevant studies underwent full-text assessment (See Appendix).

Eligibility criteria

Inclusion Criteria

Studies were eligible for inclusion if they met the following criteria: adult patients (aged ⩾18 years) undergoing cardiac surgery; use of ANH as a perioperative blood-management strategy; inclusion of a control group receiving conventional care, no ANH, or an alternative perioperative blood-management strategy; a randomized controlled trial (RCT) or comparative observational study design; reporting of at least one clinical, safety, blood-loss, or transfusion-related outcome; and availability of sufficient quantitative data to calculate effect estimates for meta-analysis.

Exclusion Criteria

Studies were excluded if they met any of the following criteria: case reports or case series without a comparator group; reviews, systematic reviews, meta-analyses, editorials, letters, or study protocols; conference abstracts with insufficient outcome data for quantitative analysis; animal studies or studies involving pediatric populations; studies involving non-cardiac surgical procedures; studies without a comparator group or relevant clinical, safety, blood-loss, or transfusion-related outcomes; duplicate publications or overlapping reports of the same study population. When multiple publications reported data from the same population, the most comprehensive and relevant report was retained.

Study selection and screening

We added all identified records to Rayyan AI for reference management, duplicate identification, and study screening. After removing duplicates, two independent reviewers (Muhammad Ayhan Amir and Muhammad Arslan Tariq) screened titles and abstracts based on the predefined eligibility criteria. The same two reviewers (Ali Sanan Ahmed and Zishan Haider Abbas) fully evaluated potentially relevant studies. If reviewers disagreed, they resolved it through discussion; unresolved disagreements were adjudicated by a third reviewer (Maisha Samiha). We described the study-selection process following the PRISMA flow diagram.

Data extraction

Two independent reviewers (Shamanpreet Kaur and Toki Babajide) carried out data extraction using a standardized data-extraction form. Reference management was carried out using Zotero version 8.0 (Corporation for Digital Scholarship, Vienna, VA). The information extracted included study characteristics, author, year of publication, study design, sample size, patient characteristics, type of cardiac surgery, ANH protocol, comparator characteristics, and relevant baseline characteristics. Outcome measures included chest tube drainage/blood loss, hospital length of stay, perioperative RBC transfusion, number of patients receiving RBC transfusion, platelet transfusion, FFP transfusion, and cardiac surgery-associated acute kidney injury (CSA-AKI). Extracted data were checked against the original articles for discrepancies, which were resolved by consensus or consultation with a third reviewer.

Quality assessment using RoB 2.0 and the Newcastle-Ottawa Scale

Two reviewers independently assessed the methodological quality of the included studies. RCTs were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool [10], which assesses five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS) [11], which evaluates selection, comparability, and outcome or exposure ascertainment. Disagreements were resolved through discussion or consultation with a third reviewer.

Statistical analysis

All statistical analyses and forest plots were generated using Review Manager (RevMan), version 5.4 (The Cochrane Collaboration, London, United Kingdom). A random-effects model was used because clinical and methodological heterogeneity was anticipated across studies. Dichotomous outcomes were pooled using risk ratios (RRs) and 95% confidence intervals (CIs) with the Mantel-Haenszel method. Continuous outcomes were pooled using mean differences (MDs) and 95% CIs when studies reported the same outcome using comparable measurement scales and units. Continuous outcomes were analyzed using the inverse-variance method. Statistical significance was defined as a two-sided P-value less than 0.05. Between-study heterogeneity was assessed using Cochran's Q test and the I^2 statistic. I^2 values of 0%-25% were interpreted as low heterogeneity, 26%-50% as moderate heterogeneity, 51%-75% as substantial heterogeneity, and greater than 75% as considerable heterogeneity. Continuous outcomes were extracted as means, standard deviations (SDs), and sample sizes. When studies reported medians and interquartile ranges instead of means and SDs, the data were converted using the meta-converter tool (metaconvert.org), provided that sufficient information was available to support the conversion. The units and definitions of continuous outcomes were checked for comparability before pooling. Studies comparing different ANH regimens were distinguished from those comparing ANH with conventional care or no ANH; the low-volume and moderate-volume ANH groups in Ming et al. [18] were treated as distinct intervention regimens and included only in appropriate analyses. Sensitivity analyses were conducted for selected outcomes by excluding studies as indicated by the sensitivity-analysis approach, and changes in effect estimates, CIs, statistical significance, and heterogeneity were evaluated. Funnel plots were used to explore potential publication bias or small-study effects for outcomes with a sufficient number of contributing studies, generally 10 or more, and were interpreted cautiously because asymmetry may have causes other than publication bias. A formal assessment of certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework was not performed; therefore, certainty ratings were not assigned, and the findings were interpreted in light of heterogeneity, sensitivity analyses, study quality, and estimate precision.

Results

Study Selection Process

We identified 1,455 records from PubMed (n = 794), Embase (n = 301), Scopus (n = 303), and the Cochrane Library (n = 57). After de-duplicating 569 records, we screened 886 records by title and abstract. We excluded 437 during preliminary screening. In total, we sought 449 reports for full-text retrieval, and two reports were not retrievable. Thus, we evaluated 447 full-text reports for eligibility. Of these, we excluded 433 reports for the wrong population (n = 254), intervention (n = 111), comparator (n = 37), or outcomes (n = 31). Finally, 14 studies were eligible and included in the SRMA (Figure *1*).

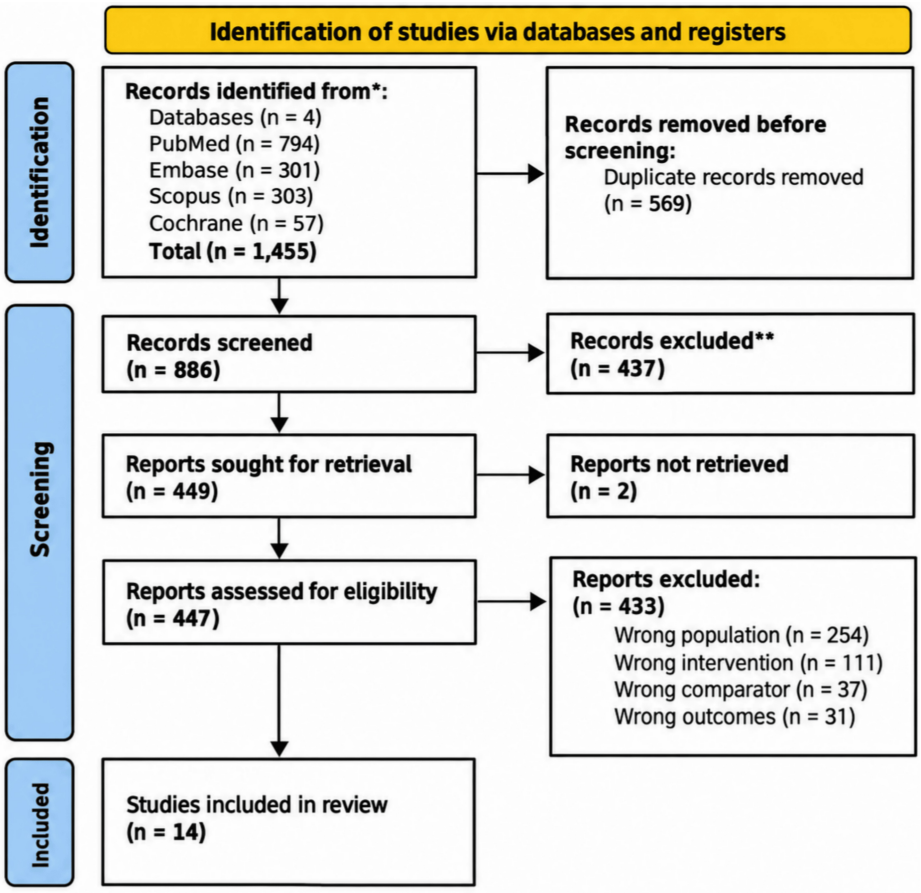


FIGURE 1: PRISMA flow diagram showing study selection

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Baseline Characteristics

Fourteen studies [12-25] evaluating ANH in adult cardiac surgery were included. The studies investigated coronary artery bypass grafting (CABG), valve surgery, complex cardiac procedures, and thoracic aortic repair, with most procedures performed using CPB. Sample sizes varied considerably, ranging from small randomized trials to large studies, including the 2,010-patient trial by Monaco et al. [16]. Baseline age, sex distribution, body weight, hemoglobin, hematocrit, and platelet counts varied across studies, with some variables not reported consistently. ANH protocols included fixed-volume, weight-based, and hematocrit-guided blood withdrawal. Reported withdrawal volumes ranged from approximately 270 to 700 mL in studies using fixed or target-based protocols, while other studies used weight-based collection. Crystalloids, colloids, or combinations of fluids were used for volume replacement. Autologous blood was generally reinfused intraoperatively, commonly after CPB or protamine administration. These differences in baseline characteristics and ANH protocols should be considered when interpreting the pooled outcomes. The detailed characteristics of the included studies are presented in Table *1*.

Study	Design and Setting	Surgical Population	Groups (n)	Age (Years)	Female, n (%)	Weight/BMI/BSA	Baseline Hb/Hct	Platelets (×10³/μL)	ANH Protocol
Licker et al., 2005 [12]	Prospective RCT; Switzerland	Elective CABG on CPB	ANH: 41; Control: 39	67 (63–70); 65 (62–68)	8 (19.5%); 6 (15.4%)	BSA: 2.7; 2.8 m²	Hct: 41.0 ± 6.3%; 40.0 ± 6.2%	NR; NR	Target Hct 28%–30%; 6% HES; reinfusion during CPB
Licker et al., 2007 [13]	Prospective RCT; Switzerland	AVR for severe aortic stenosis	ANH: 19; Control: 21	68 ± 9; 65 ± 10	6 (31.6%); 6 (28.6%)	NR	Hb: 14.5 ± 0.9; 14.3 ± 1.0 g/dL	NR; NR	Target Hct 28%–30%; 6% HES; reinfusion during/after CPB weaning
Lubin et al., 2025 [14]	Prospective RCT; USA	Complex cardiac surgery on CPB	ANH: 32; Control: 29	50.9 ± 18.6; 60.3 ± 14.8	8 (25.0%); 9 (31.0%)	Weight: 83.6 ± 20.1; 85.7 ± 21.6 kg	Hb: 13.6 ± 1.5; 13.5 ± 1.7 g/dL	224.9 ± 47.1; 197.4 ± 61.8	8–10 mL/kg, maximum 700 mL; crystalloid/colloid 1:1; reinfusion after CPB/protamine
Mahoori et al., 2009 [15]	Prospective RCT; Iran	Elective CABG on CPB	ANH: 54; Control: 47	55 ± 12; 58 ± 9	8 (14.8%); 7 (14.9%)	Weight: 67.5 ± 14.2; 71.9 ± 11.4 kg	Hb: 13.7 ± 1.0; 13.2 ± 1.0 g/dL	230.9 ± 62.0; 257.4 ± 10.0	10% blood volume; modified gelatin; reinfusion at the end of CPB
Monaco et al., 2025 [16]	Phase 3 multicenter RCT; 32 centers, 11 countries	Elective on-pump cardiac surgery	ANH: 1,010; Usual care: 1,000	59 (52–66); 61 (53–68)	219 (21.7%); 186 (18.6%)	Weight: 79 (69–90); 80 (70–90) kg	Hb: 14 (14–15); 15 (14–15) g/dL	208 (173–252); 210 (177–246)	Target ≥ 650 mL; crystalloids as needed; reinfusion after CPB weaning/protamine
Okazawa et al., 2026 [17]	Retrospective database cohort; Japan	Adult elective cardiac surgery	ANH: 1,644; non-ANH: 1,639	69 (59–75); 69 (58–76)	418 (25.0%); 414 (25.0%)	BMI: 23.5; 23.3 kg/m²	NR; anemia 3% in each group	NR; NR	Routine practice; fluid at institutional discretion; intraoperative reinfusion
Ming et al., 2023 [18]	Dose-comparison RCT; China	Elective on-pump cardiac surgery	Low-volume: 55; moderate-volume: 55	18–75; 18–75	NR; NR	Eligibility weight ≥ 50 kg	Hb: 14.3 ± 1.3; 14.3 ± 1.2 g/dL	183 ± 50; 188 ± 41	5–8 vs 12–15 mL/kg as reported; fluid formula and reinfusion after CPB separation
Ela et al., 2009 [19]	Double-blind RCT; Turkey	Elective off-pump CABG	AHBT: 28; ABT: 29	64.2 ± 8.3; 62.1 ± 7.4	6 (21.4%); 5 (17.2%)	NR	Hb: 15.1 ± 1.9; 14.7 ± 1.8 g/dL	218 ± 71; 225 ± 63	400–700 mL; 6% HES; reinfusion after grafting
Jalali et al., 2008 [20]	Prospective RCT; Iran	Elective CABG on CPB	ANH: 50; Control: 50	54.7 ± 8.4; 58.6 ± 9.1	1 (2.0%); 6 (12.0%)	NR	Hct: 45.1 ± 2.4%; 44.1 ± 2.7%	208 ± 54; 219 ± 57	Hemodynamically guided; normal saline; reinfusion before leaving OR
Mladinov et al., 2021 [21]	Observational cohort; USA	Thoracic aortic repair on CPB	ANH: 89; No ANH: 116	58.4 ± 13.4; 57.8 ± 14.8	20 (22.5%); 34 (28.7%)	Weight: 94.8 ± 22.9; 92.2 ± 22.2 kg	Hb: 13.8 ± 1.5; 13.7 ± 1.7 g/dL	219.3 ± 64.4; 203.9 ± 69.2	Pragmatic pre-CPB phlebotomy; crystalloids/colloids; reinfusion after CPB
Momeni et al., 2012 [22]	Three-arm prospective RCT; Belgium	Elective CABG on CPB	ANH: 30; CPB control: 31	66 ± 8; 61 ± 9	1 (3.3%); 5 (16.1%)	NR	Hb: 14.0 ± 1.0; 14.4 ± 1.0 g/dL	NR; NR	Weight/Hct-based volume; 6% Volulyte; Hct-guided reinfusion
Soltanzadeh et al., 2012 [23]	Double-blind RCT; Iran	Elective CABG; all-male cohort	Autologous: 50; Control: 50	NR; eligibility: <70 years	0 (0%); 0 (0%)	NR; eligibility: BMI < 24 kg/m²	NR; eligibility: Hb > 12 g/dL	NR; eligibility > 100 (unit to verify)	500 mL; Ringer's lactate; reinfusion after protamine
Tanaka et al., 2025 [24]	Retrospective registry cohort; USA	Adult cardiac surgery	16,795; 14.7% received ANH	NR	NR	NR	NR	NR	Registry data; clinician-directed fluids and post-bypass reinfusion
Virmani et al., 2010 [25]	Prospective RCT; India	Elective valve surgery on CPB	ANH: 88; Control: 100	31.1 ± 11.9; 30.9 ± 10.6	40 (45.5%); 55 (55.0%)	Weight: 47.7 ± 8.8; 46.2 ± 10.1 kg	Hb: 12.4 ± 1.4; 12.1 ± 1.6 g/dL	180 ± 50; 190 ± 60	7%–10% estimated blood volume according to Hb; 6% HES; reinfusion after protamine

TABLE 1: Baseline characteristics and patient's demography of included studies

Notes: ABT: Autologous blood transfusion; AHBT: Autologous hemoblood transfusion; ANH: Acute normovolemic hemodilution; AVR: Aortic valve replacement; BMI: Body mass index; BSA: Body surface area; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; Hb: Hemoglobin; Hct: Hematocrit; HES: Hydroxyethyl starch; NR: Not reported; OR: Operating room; RCT: Randomized controlled trial.

RoB 2.0 Assessment

The RoB 2.0 assessment involved 11 studies evaluating the use of ANH in cardiac surgery. Monaco et al. [16], Ming et al. [18], Ela et al. [19], and Virmani et al. [25] were judged to have an overall low risk of bias across all domains. Licker et al. [12] and Licker et al. [13] raised a few concerns, primarily about deviations from the intended intervention. Lubin et al. (2025) [14] also noted some of these concerns across multiple domains. Momeni et al. [22] and Jalali et al. [20] raised some overall concerns, while Soltanzadeh et al. [23] raised none. The only study with a high overall risk of bias was Mahoori et al. [15] for missing outcome data and selection of reported data. Four studies had a low risk of bias, six had some concerns, and one had a high risk of bias, suggesting generally good methodological quality (Figures *2*, *3*).

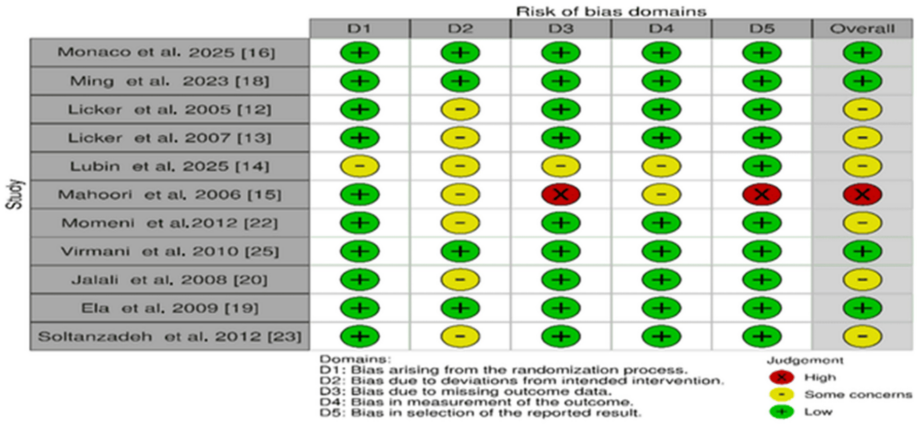


FIGURE 2: Traffic plot of risk of bias assessment using RoB 2.0

RoB: Risk of Bias.

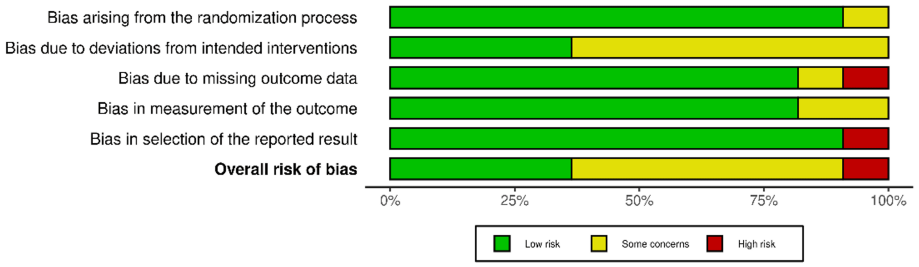


FIGURE 3: Summary plot of risk of bias assessment using RoB 2.0

RoB: Risk of Bias.

Quality Assessment of the Included Studies Using Newcastle-Ottawa Scale

The methodological quality of the three observational studies was assessed using the NOS. Okazawa et al. [17] and Tanaka et al. [24] achieved the maximum score of 9/9 stars, indicating high methodological quality according to the reported assessments. Both studies received stars across the selection and outcome domains, as well as for comparability, suggesting that their study design and analytical approaches addressed the assessed quality criteria. Mladinov et al. [21] received 7/9 stars, indicating comparatively lower methodological quality, primarily due to fewer stars awarded in the comparability and outcome domains. Overall, the NOS assessments suggested that the included observational studies were of generally good methodological quality, although some differences in study quality were evident. These differences should be considered when interpreting the pooled findings, particularly because observational studies may remain susceptible to residual confounding and selection bias despite statistical adjustment. The NOS scores should therefore be interpreted as indicators of methodological quality rather than definitive evidence that bias was absent (Table *2*).

Study ID	Selection: Exposed Cohort	Selection: Non-exposed	Selection: Ascertainment	Selection: Outcome Not Present	Comparability: Design and Analysis	Outcomes: Assessment and Follow-Up	Total Stars (Quality)
Okazawa et al., 2026 [17]	★	★	★	★	★★	★★★	9/9
Tanaka et al., 2025 [24]	★	★	★	★	★★	★★★	9/9
Mladinov et al., 2021 [21]	★	★	★	★	★☆	★★☆	7/9

TABLE 2: Quality assessment of the included studies using Newcastle-Ottawa Scale

NOS: Newcastle–Ottawa Scale; ★: Awarded star; ☆: Criterion not awarded.

Meta-analysis of outcomes

Chest Tube Drainage

A total of eight studies [12,13,15,16,19-21,25] were included in the analysis, comprising 2,773 patients (1,374 in the ANH group and 1,399 in the control group). The pooled analysis showed that ANH significantly reduced postoperative chest tube drainage compared with the control group (MD = −66.74 mL, 95% CI: −121.45 to −12.02; P = 0.02). Substantial heterogeneity was observed among the included studies (I^2 = 93%), indicating considerable variability in the study results (Figure *4*).

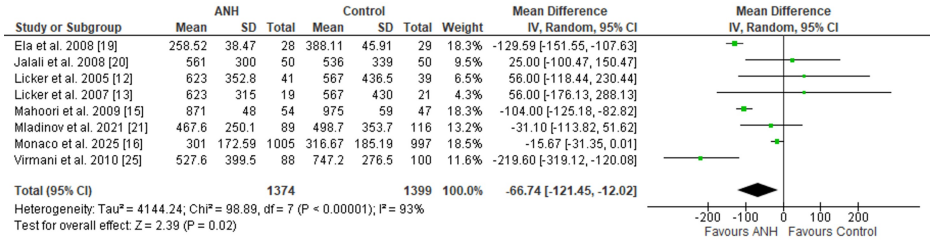


FIGURE 4: Forest plot of chest tube drainage

Sensitivity Analysis of Chest Tube Drainage

Following the removal of the study by Monaco et al. [16] included in the sensitivity analysis, seven studies involving 771 patients (369 in the ANH group and 402 in the control group) were analyzed. ANH was associated with a significant reduction in postoperative chest tube drainage compared with the control group (MD = −90.70 mL, 95% CI: −133.09 to −48.31; P < 0.0001). However, substantial heterogeneity remained (I^2 = 72%). These findings indicate that the reduction in chest tube drainage remained statistically significant after study removal, although heterogeneity persisted (Figure *5*).

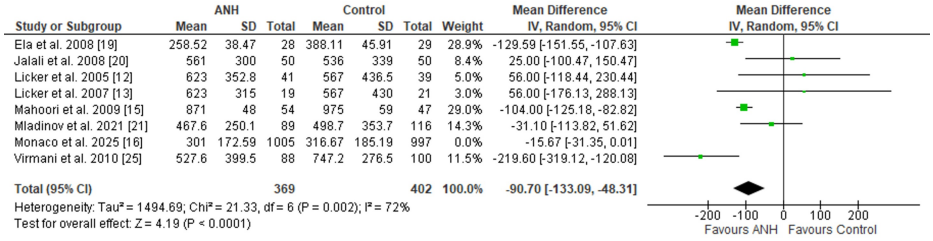


FIGURE 5: Forest plot of sensitivity analysis of chest tube drainage

Publication Bias for Chest Tube Drainage

Visual inspection of the funnel plot suggested an asymmetric distribution of the included studies around the pooled MD, with studies scattered on both sides and a relatively uneven spread across the range of standard errors. This asymmetry may indicate potential small-study effects or publication bias. However, given the small number of studies included, these findings should be interpreted cautiously, and publication bias cannot be confirmed based on visual inspection alone (Figure 6).

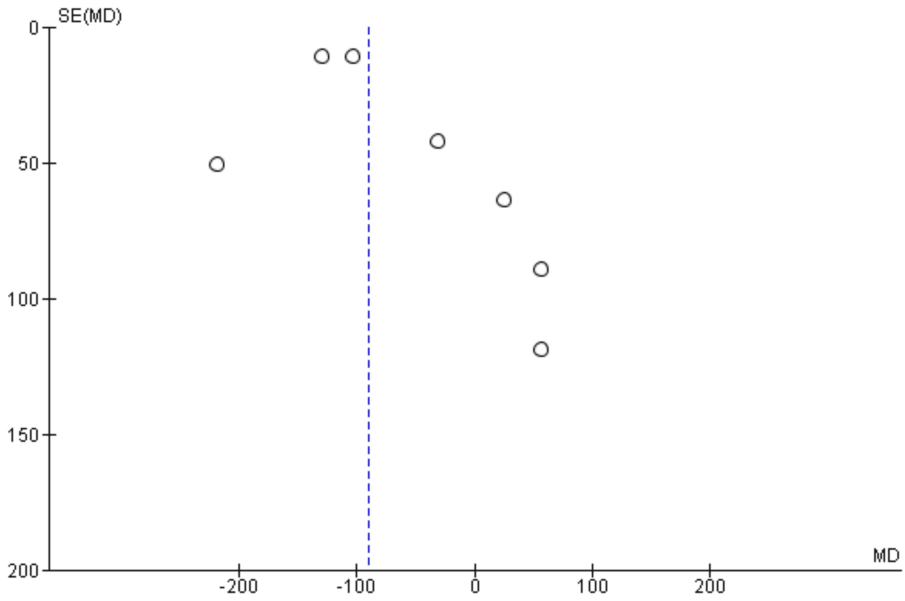


FIGURE 6: Publication bias for chest tube drainage

Hospital Length of Stay in Days

Seven studies [12-14,16-19] involving 2,824 patients in the ANH group and 2,807 patients in the control group were included in the analysis. ANH was associated with a significantly shorter hospital stay compared with the control group (MD = −0.75 days, 95% CI: −1.00 to −0.51; P < 0.00001). However, substantial heterogeneity was observed among the included studies (I^2 = 92%). These findings indicate that ANH significantly reduced hospital length of stay, although considerable variability existed across studies (Figure 7).

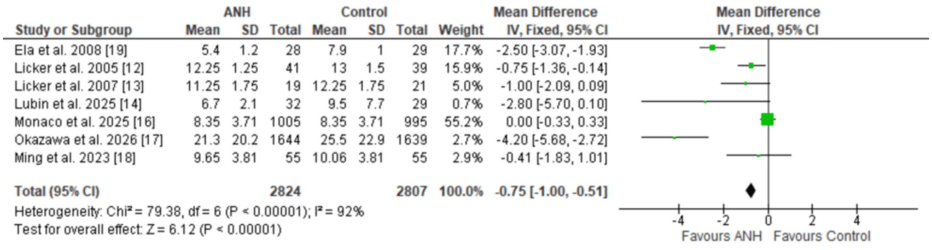


FIGURE 7: Forest plot of hospital length of stay in days

Sensitivity Analysis of Hospital Length of Stay in Days

Following the exclusion of Monaco et al. [16], six studies involving [12-14,17-19] 1,819 patients in the ANH group and 1,812 patients in the control group were analyzed. ANH was associated with a significantly shorter hospital stay compared with the control group (MD = −1.82 days, 95% CI: −2.90 to −0.74; P = 0.0009). Substantial heterogeneity persisted among the included studies (I^2 = 85%). These findings indicate that the reduction in hospital length of stay remained statistically significant after study exclusion, although considerable heterogeneity persisted (Figure 8).

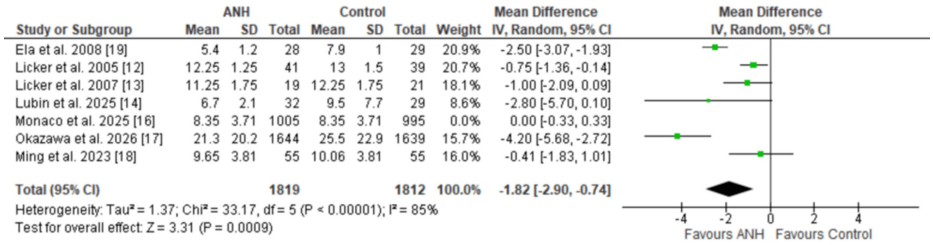


FIGURE 8: Sensitivity analysis of hospital length of stay in days

Publication Bias for Hospital Length of Stay in Days

Visual inspection of the funnel plot for hospital length of stay showed some asymmetry in the distribution of the included studies around the pooled effect estimate. Several studies were distributed within the funnel boundaries, while others fell outside them, particularly on the left side. This pattern may suggest potential small-study effects or publication bias (Figure *9*).

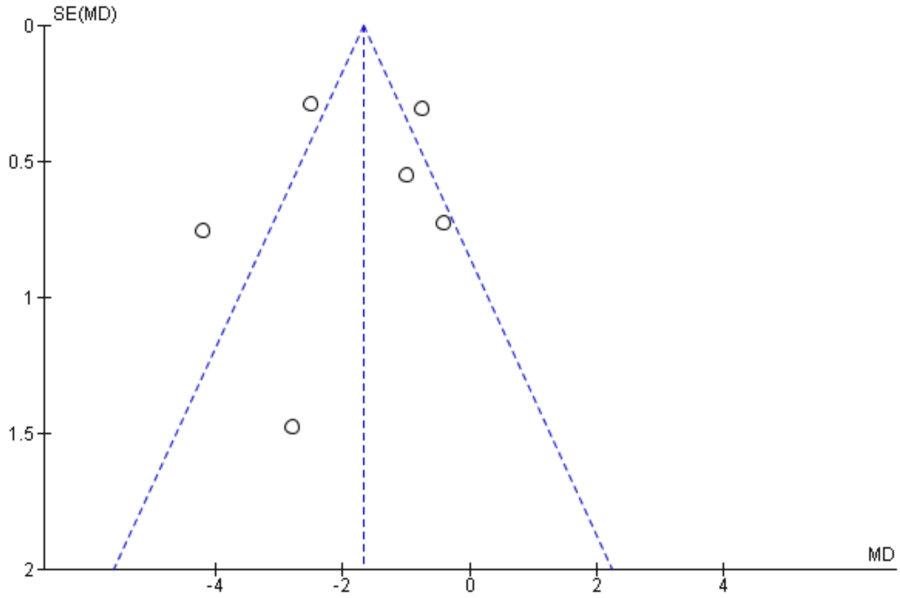


FIGURE 9: Publication bias for hospital length of stay in days

Patients Receiving Blood Transfusion

The pooled analysis of nine studies [12,13,15,16,18-20,22,24] involving 3,564 patients in the ANH group and 3,551 patients in the control group showed a significantly lower risk of blood transfusion in the ANH group (RR = 0.73, 95% CI: 0.57-0.93; P = 0.01). However, substantial heterogeneity was observed among the included studies (I^2 = 78%). These findings suggest that ANH was associated with a reduced risk of blood transfusion in the overall analysis, although considerable heterogeneity was present (Figure *10*).

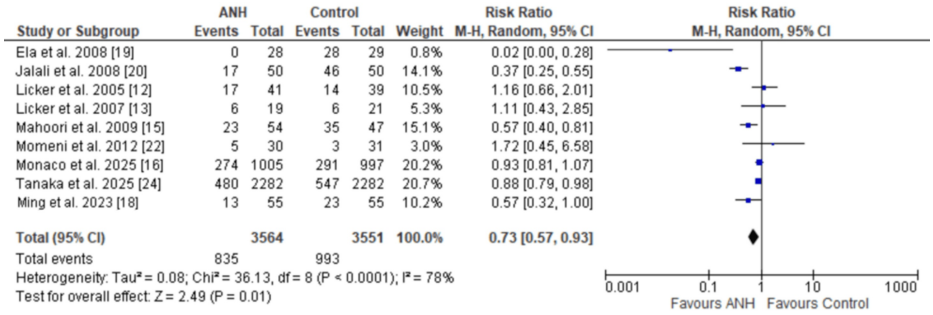


FIGURE 10: Forest plot of patients receiving blood transfusion

Sensitivity Analysis of Patients Receiving Blood Transfusion

The pooled analysis of eight studies involving 3,514 patients in the ANH group and 3,501 patients in the control group showed no statistically significant difference in the risk of blood transfusion between the groups (RR = 0.82, 95% CI: 0.67-1.01; P = 0.06). Substantial heterogeneity was observed among the included studies (I^2 = 63%). These findings suggest that the difference in blood transfusion risk between ANH and control groups did not reach statistical significance (Figure *11*).

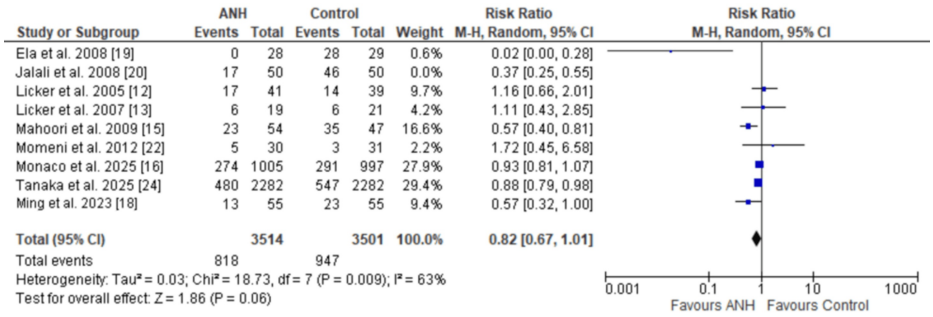


FIGURE 11: Forest plot of sensitivity analysis of patients receiving blood transfusion

Visual inspection of the funnel plot for patients receiving blood transfusion suggested asymmetry in the distribution of studies around the pooled RR, with one study markedly separated from the remaining studies in the lower-left region and an uneven distribution of the other studies. This pattern may indicate potential small-study effects or publication bias. However, given the limited number of included studies (nine), the findings should be interpreted cautiously, as visual inspection alone cannot confirm publication bias (Figure *12*).

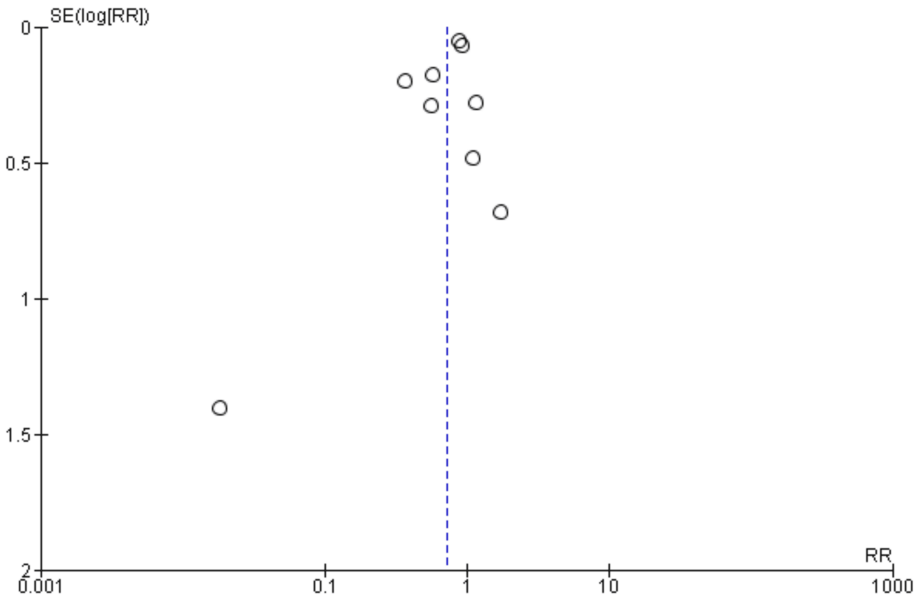


FIGURE 12: Publication bias for patients receiving blood transfusion

Perioperative RBC Transfusion

The pooled analysis of 10 studies [12-15,18,20,22-25] involving 2,663 patients in the ANH group and 2,654 patients in the control group demonstrated a statistically significant difference favoring ANH (MD = −0.34, 95% CI: −0.61 to −0.07; P = 0.01). Substantial heterogeneity was observed among the included studies (I^2 = 85%). These findings suggest a significant reduction in the reported perioperative RBC transfusion outcome with ANH compared with the control group (Figure *13*).

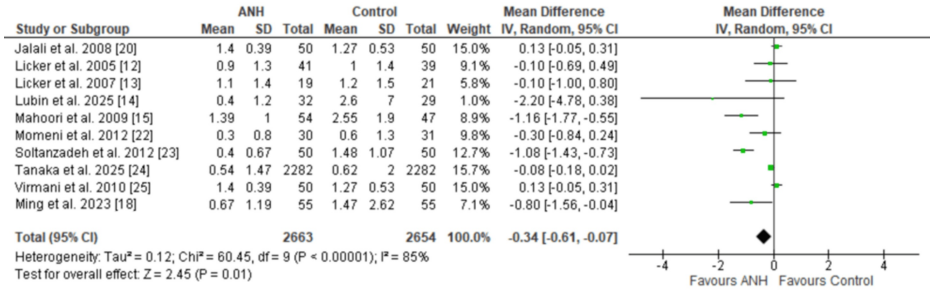


FIGURE 13: Forest plot of perioperative RBC transfusion

Sensitivity Analysis of Perioperative RBC Transfusion

Following the exclusion of Mahoori et al. [15], nine studies [12-14,18,20,22-25] involving 2,609 patients in the ANH group and 2,607 patients in the control group were analyzed in the sensitivity analysis. ANH was associated with a reduction in perioperative RBC transfusion compared with the control group; however, the difference was not statistically significant (MD = −0.25, 95% CI: −0.51 to 0.01; P = 0.06). Substantial heterogeneity persisted among the included studies (I^2 = 83%). These findings indicate that the reduction in perioperative RBC transfusion was no longer statistically significant following study exclusion, suggesting that the original finding may be sensitive to the removal of an individual study (Figure *14*).

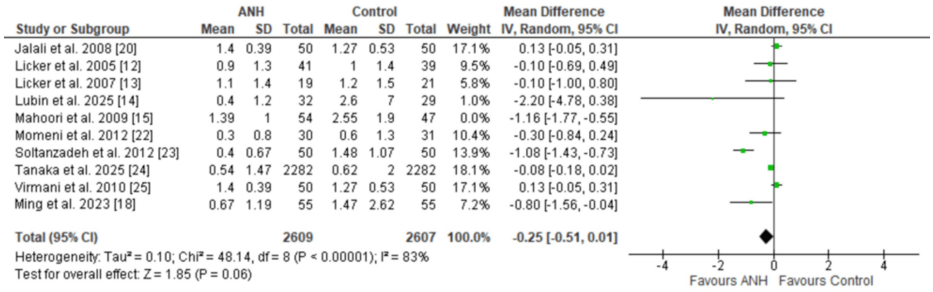


FIGURE 14: Forest plot of sensitivity analysis of perioperative RBC transfusion

Publication Bias Assessment of Perioperative RBC Transfusion

Visual inspection of the funnel plot for perioperative RBC transfusion suggested potential asymmetry, with most studies clustered around the pooled effect estimate and one study positioned considerably farther to the left in the lower part of the plot. This pattern may indicate small-study effects or potential publication bias. However, given the limited number of included studies (10), the findings should be interpreted cautiously, as funnel plot asymmetry alone cannot establish the presence of publication bias (Figure *15*).

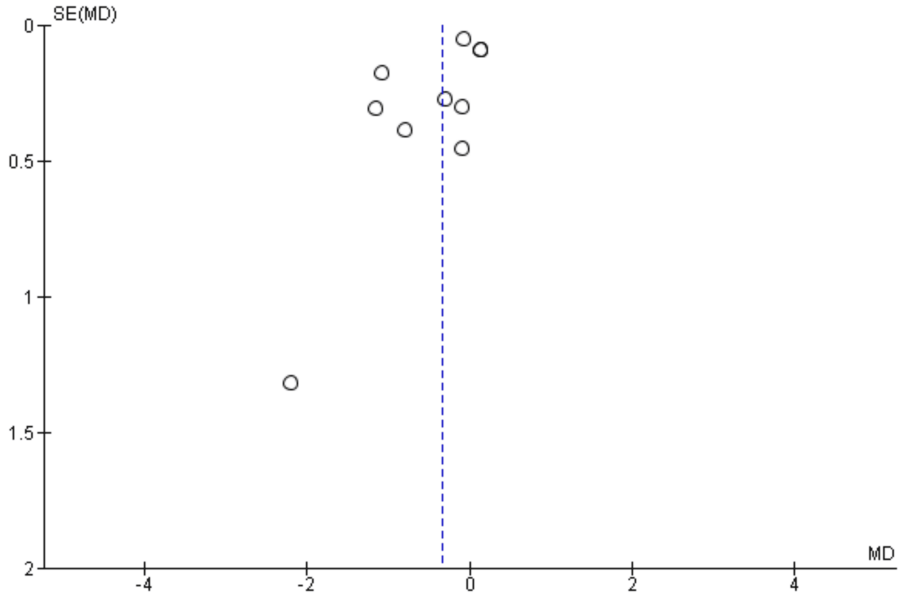


FIGURE 15: Publication bias for perioperative RBC transfusion

CSA-AKI

Five studies [12,16,17,18,21] involving 5,679 patients (2,834 in the ANH group and 2,845 in the control group) were included in the analysis. The pooled results showed no statistically significant difference in the risk of CSA-AKI between the ANH and control groups (RR = 0.84, 95% CI: 0.67-1.06; P = 0.15). No significant heterogeneity was observed among the included studies ($I^2 = 0\%$; $\tau^2 = 0.00$; $\chi^2 = 3.82$, P = 0.43). These findings suggest that ANH was not associated with a statistically significant reduction in the risk of CSA-AKI compared with the control group (Figure *16*).

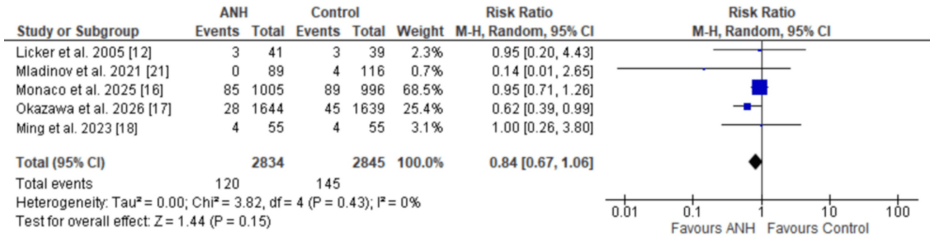


FIGURE 16: Forest plot of cardiac surgery-associated acute kidney injury

Patients Receiving Allogeneic Platelet Transfusion

We included four studies [15,16,18,21] with 2,418 patients (1,203 in the ANH group and 1,215 in the control group). The number of patients receiving platelet transfusion was 106 in the ANH group and 122 in the control group. There was no statistically significant difference in the risk of requiring platelet transfusion between the ANH and control groups (RR = 0.95, 95% CI: 0.72-1.25; P = 0.69) in the pooled analysis. There was low heterogeneity between the studies (I^2 = 24%), as shown in Figure *17*.

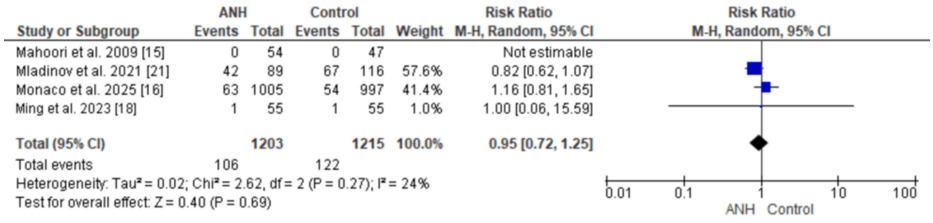


FIGURE 17: Forest plot of patients receiving allogeneic platelet transfusion

Discussion

Principal Findings

This SRMA evaluated the efficacy and safety of ANH in adult cardiac surgery. The findings suggest that ANH may be a useful blood-conservation strategy, particularly for reducing postoperative chest tube drainage, hospital length of stay, and perioperative RBC transfusion volume. However, the robustness of the transfusion-related findings was limited by the sensitivity analyses. Although the overall analysis showed a significantly lower proportion of patients receiving RBC transfusions, this difference was no longer statistically significant after sensitivity analysis. Similarly, the reduction in perioperative RBC transfusion volume did not remain statistically significant after study exclusion. ANH was not associated with statistically significant differences in CSA-AKI or allogeneic platelet transfusion. These findings support the potential role of ANH within multimodal PBM while highlighting uncertainty regarding the consistency and magnitude of its benefits across different clinical settings.

Comparison With Previous Literature

The findings of the present meta-analysis are broadly consistent with previous evidence suggesting that ANH can contribute to blood conservation during cardiac surgery. The underlying rationale is that blood removed before major surgical blood loss contains a relatively high concentration of RBCs, which can subsequently be returned to the patient after the period of greatest bleeding risk. By reducing the loss of circulating RBCs during surgery, ANH may reduce the need for allogeneic transfusion. Earlier meta-analyses by Li et al. and Barile et al. reported reductions in RBC transfusion requirements and postoperative blood loss, supporting the potential value of ANH in cardiac surgical practice [26,27]. However, the magnitude and consistency of these benefits have varied across reviews, indicating that the effectiveness of ANH may depend on patient selection, the volume of blood withdrawn, the type of operation, and the accompanying blood management strategies.

More recent evidence has reinforced this uncertainty. In a contemporary meta-analysis restricted to RCTs, Pruna et al. found that ANH did not significantly reduce the overall proportion of patients receiving allogeneic RBC transfusions during postoperative hospitalization, although a reduction was observed in

transfusions administered during the first 48 postoperative hours [28]. This distinction is important because ANH may have its greatest effect during the intraoperative and immediate postoperative periods, when reinfusion of collected autologous blood can directly support circulating red cell mass. Transfusions later during hospitalization may instead be influenced by persistent anemia, delayed bleeding, postoperative complications, and local transfusion thresholds. Consequently, a reduction in early transfusion exposure does not necessarily translate into a consistent reduction in the proportion of patients transfused over the entire hospital stay [28].

The large contemporary randomized trial by Monaco et al. also highlights the need to reassess the incremental benefit of ANH within modern cardiac surgical practice [16]. Although the physiological rationale for ANH remains plausible, its effectiveness must be considered in the context of contemporary PBM, including preoperative anemia assessment and treatment, restrictive transfusion strategies, antifibrinolytic therapy, cell salvage, and targeted management of coagulopathy. These interventions can independently reduce allogeneic transfusion and may leave less room for ANH to provide an additional benefit. Therefore, differences between earlier meta-analyses and more recent evidence may partly reflect changes in usual care, as well as variation in trial design and outcome definitions. The available evidence does not, however, establish that any single component of modern PBM explains the differences between pooled results [16].

In the present analysis, ANH was associated with lower postoperative chest tube drainage. This finding is directionally consistent with the earlier meta-analyses by Li et al. and Barile et al., which reported reductions in postoperative blood loss among patients receiving ANH [26,27]. Nevertheless, the substantial heterogeneity in the present analysis, which persisted after sensitivity analysis, indicates that the observed effect was not uniform across studies. Differences in surgical complexity, CPB management, the volume and timing of blood collection, fluid replacement strategies, anticoagulation reversal, and chest drainage protocols may have contributed to the variability. In addition, chest tube drainage represents a specific measure of postoperative blood loss rather than total perioperative blood loss. It should therefore be interpreted alongside, rather than as a substitute for, transfusion requirements and other clinically important bleeding outcomes. The recent evidence synthesis by Alam et al. further illustrates that estimates for transfusion-related outcomes and bleeding outcomes do not necessarily move in parallel across studies [29].

The association between ANH and shorter hospital length of stay should also be interpreted cautiously. Although the overall analysis favored ANH, the estimated effect changed after exclusion of Monaco et al. [16], indicating that the pooled result was sensitive to the influence of an individual study. This sensitivity may reflect differences in patient characteristics, perioperative pathways, surgical risk, discharge practices, or the implementation of other blood conservation measures. A shorter hospital stay could plausibly arise if a blood conservation strategy reduces clinically consequential anemia or transfusion-related complications; however, the present findings do not establish this causal pathway. Length of stay is a multifactorial outcome, and it is particularly susceptible to differences in healthcare systems and institutional discharge criteria. Accordingly, the finding should be considered a potentially favorable association requiring confirmation rather than definitive evidence that ANH independently accelerates postoperative recovery [16].

The effects of ANH on RBC transfusion incidence and transfusion quantity warrant particular attention. In the present analysis, the reduction in the proportion of patients receiving RBC transfusions was not robust to sensitivity analysis. Similarly, the apparent reduction in perioperative RBC transfusion quantity did not remain statistically significant after exclusion of the influential study. These findings suggest that the primary pooled estimates should not be interpreted as conclusive evidence of a consistent transfusion benefit across all included populations. Rather, they indicate that the apparent effect may depend partly on the studies included and the clinical settings in which ANH was implemented.

This interpretation is consistent with the variation observed in contemporary systematic reviews. While Li et al. and Barile et al. reported favorable transfusion findings in earlier analyses, Pruna et al. found no statistically significant reduction in overall postoperative transfusion incidence when the observation period extended beyond the immediate postoperative phase [26-28]. In contrast, the 2026 review by Alam et al. [29] reported favorable findings across several transfusion-related outcomes, while another contemporary synthesis by Elfiki et al. found that the apparent reduction in transfusion incidence was less conclusive when the analysis was restricted to randomized trials [29,30]. These differences illustrate why the overall direction of a pooled estimate should not be considered in isolation. Study eligibility, the balance between randomized and observational evidence, definitions of transfusion outcomes, follow-up duration, and analytical decisions can materially influence the conclusions of a meta-analysis.

The distinction between the incidence and quantity of transfusion is also methodologically important. Transfusion incidence indicates whether a patient received any allogeneic RBCs, whereas transfusion quantity reflects the number of units administered. An intervention may reduce the number of units given to patients who require transfusion without preventing transfusion in a substantial proportion of patients. Conversely, the proportion of patients transfused may decrease without a comparable reduction in the average number of units administered. These outcomes should therefore be reported and interpreted

separately. Before publication, the precise definition and unit of the continuous perioperative RBC transfusion outcome in the present analysis should be verified to ensure that the pooled MD is clinically interpretable.

For platelet transfusion, the present analysis did not identify a statistically significant difference between ANH and control groups. This finding should be interpreted as inconclusive evidence of a difference rather than proof that the two approaches are equivalent. Platelet transfusion is determined by several factors beyond red cell loss, including platelet dysfunction associated with CPB, pre-existing antiplatelet therapy, coagulation abnormalities, and the severity of surgical bleeding. Similarly, the effect of ANH on FFP transfusion should be interpreted separately from its effect on RBC transfusion. Plasma administration is generally guided by evidence of coagulation factor deficiency or clinically significant coagulopathy rather than by anemia alone. The contemporary review by Elfiki et al. did not identify a significant difference in FFP transfusion, illustrating that the effect of ANH may not extend equally to all blood components [30]. The specific conclusion for FFP in the present study should be finalized only after its pooled estimate and CI have been verified.

Regarding renal safety, the present analysis did not demonstrate a statistically significant difference in CSA-AKI between ANH and control groups. The absence of substantial statistical heterogeneity suggests greater consistency across the included estimates, but it does not establish equivalence or exclude clinically relevant benefit or harm. ANH reduces hematocrit during the period before reinfusion, and the clinical consequences of this reduction may depend on baseline hemoglobin, renal function, hemodynamic stability, oxygen delivery during CPB, and the degree of hemodilution. The contemporary synthesis by Elfiki et al. likewise did not identify a significant difference in renal dysfunction, providing some reassurance while leaving uncertainty about uncommon or subgroup-specific effects [30]. Future studies should use standardized AKI definitions and prospectively assess renal outcomes, particularly among patients with pre-existing kidney disease or limited physiological reserve.

The clinical implications of these findings align with current PBM guidance. The 2021 Society of Thoracic Surgeons, the Society of Cardiovascular Anesthesiologists, the American Society of ExtraCorporeal Technology, and the Society for the Advancement of Patient Blood Management guidelines recognize ANH as a reasonable blood conservation option in selected patients undergoing cardiac surgery [31]. The updated European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology and Intensive Care guidelines similarly discuss ANH within the broader framework of perioperative blood conservation while emphasizing the importance of patient characteristics, hemodilution, and integration with other PBM interventions [32]. These recommendations support considering ANH as one component of an individualized strategy rather than as a universal intervention expected to produce the same benefit in every patient. In particular, the anticipated benefit should be balanced against the patient's baseline hemoglobin, anticipated surgical blood loss, hemodynamic tolerance, and the amount of blood that can safely be collected and reinfused [32,33].

Overall, the present findings support a cautious interpretation of ANH's role in contemporary cardiac surgery. The observed reductions in postoperative drainage and the favorable primary estimates for RBC transfusion suggest potential benefits. Still, sensitivity analyses demonstrate that some effects are not consistently maintained when influential studies are excluded. The findings for platelet transfusion and CSA-AKI do not establish either equivalence or definitive safety across all patient groups. Differences in ANH protocols, transfusion triggers, operative procedures, co-interventions, and outcome definitions remain important sources of clinical and methodological heterogeneity. Further adequately powered randomized trials should standardize ANH protocols and transfusion thresholds, distinguish intraoperative from postoperative transfusion outcomes, and report patient-centered outcomes such as major bleeding, AKI, complications, and length of stay. Such evidence would help clarify which patients are most likely to benefit from ANH and whether its incremental value persists when contemporary PBM practices are consistently applied.

Strengths and Limitations

This SRMA has several strengths. It provides a comprehensive assessment of the clinical effectiveness and safety of ANH in adult cardiac surgery, considering multiple clinically relevant outcomes, including RBC transfusion, postoperative chest tube drainage, hospital length of stay, platelet transfusion, and CSA-AKI. The inclusion of sensitivity analyses allowed us to examine the robustness of the pooled findings and identify outcomes influenced by individual studies. Publication bias was also assessed using funnel plots for outcomes with a sufficient number of contributing studies, improving the transparency of the evidence synthesis. Furthermore, the findings were compared with previous systematic reviews and contemporary evidence to contextualize the potential role of ANH in current PBM practices.

Several limitations should be acknowledged. First, substantial heterogeneity was observed in some outcomes, potentially reflecting differences in patient characteristics, surgical procedures, ANH protocols, transfusion thresholds, and perioperative blood management practices. Second, sensitivity analyses showed that the statistical significance of some findings changed following the exclusion of individual studies,

indicating that these results should be interpreted cautiously, despite no major change in the overall interpretation of the evidence. Third, funnel plot assessments have limited reliability when relatively few studies contribute to an outcome; therefore, publication bias cannot be definitively confirmed or excluded. Fourth, differences in outcome definitions and reporting across studies may have limited direct comparability, particularly for transfusion quantity and postoperative blood loss. Fifth, a formal GRADE assessment was not performed, limiting the ability to provide a structured rating of certainty for each outcome. Finally, the available evidence may not adequately establish whether the effects of ANH differ across specific patient subgroups, surgical procedures, or levels of baseline anemia. These limitations highlight the need for cautious interpretation and further well-designed RCTs using standardized protocols and outcome definitions.

Clinical Implications

ANH may be considered as part of a comprehensive PBM strategy for appropriately selected adults undergoing cardiac surgery. Its potential value should be evaluated alongside preoperative anemia optimization, restrictive transfusion thresholds, antifibrinolytic therapy, cell salvage, and individualized coagulation management [3]. Patient selection is particularly important because the benefit-risk balance may depend on baseline hemoglobin concentration, expected blood loss, cardiovascular reserve, and the degree of hemodilution. Patients with limited hematologic or physiological reserve may be less suitable for substantial blood withdrawal, and the decision to use ANH should account for hemodynamic stability and adequate oxygen delivery.

The present results support a potential reduction in postoperative chest tube drainage and hospital length of stay, but these outcomes were associated with substantial heterogeneity. The evidence for reducing the proportion of patients receiving RBC transfusions is less robust because statistical significance was not maintained in sensitivity analysis. The absence of a statistically significant difference in CSA-AKI is reassuring but does not eliminate the need for careful perioperative monitoring. Decisions regarding ANH should therefore be individualized and integrated into established blood-conservation protocols.

Future Research

Future studies should identify the patient populations most likely to benefit from ANH and establish more consistent implementation protocols. Large multicenter RCTs should standardize blood withdrawal volumes, replacement fluids, timing of reinfusion, transfusion thresholds, CPB management, antifibrinolytic treatment, and cell salvage practices. Studies should stratify results by baseline hemoglobin concentration, surgical procedure, operative complexity, and the degree of hemodilution. Future trials should distinguish the proportion of patients receiving transfusions from the number of RBC units transfused and report outcomes separately for the intraoperative period, the first 48 postoperative hours, and the entire hospital stay. This would help determine whether the principal benefit of ANH is concentrated in the immediate perioperative period. Further studies should also assess patient-centered outcomes, including reoperation for bleeding, ICU and hospital length of stay, renal complications, neurological events, infection, mortality, and cost-effectiveness. Individual-patient-data meta-analyses may help identify treatment-effect modifiers and refine patient-selection criteria.

Conclusions

ANH may offer potential benefits as a blood conservation strategy in adult cardiac surgery, particularly in reducing postoperative chest tube drainage and possibly shortening hospital length of stay. However, the apparent reductions in RBC transfusion incidence and perioperative transfusion quantity were not robust in sensitivity analyses, limiting the certainty of these findings. No statistically significant differences were identified in platelet transfusion or CSA-AKI. However, these results should not be interpreted as definitive evidence of equivalence or safety in all patient groups. Overall, ANH should be considered an individualized component of multimodal PBM rather than a universal intervention. Further high-quality randomized controlled trials using standardized ANH protocols, transfusion thresholds, and outcome definitions are needed to establish its clinical benefits, safety, and the patient populations most likely to benefit.

Appendices

PubMed	Embase	Scopus	Cochrane
794	301	303	57
("Hemodilution"[MeSH Terms] OR "acute normovolemic hemodilution"[Title/Abstract] OR "acute normovolaemic hemodilution"[Title/Abstract] OR "acute normovolemic haemodilution"[Title/Abstract] OR "acute normovolaemic haemodilution"[Title/Abstract] OR "normovolemic hemodilution"[Title/Abstract] OR "normovolaemic haemodilution"[Title/Abstract] OR "isovolemic hemodilution"[Title/Abstract] OR "isovolaemic haemodilution"[Title/Abstract] OR "ANH"[Title/Abstract]) AND ("Cardiac Surgical Procedures"[MeSH Terms] OR "Cardiac Surgery"[Title/Abstract] OR "heart surgery"[Title/Abstract] OR "cardiac surgical"[Title/Abstract] OR "cardiopulmonary bypass"[Title/Abstract] OR "CPB"[Title/Abstract] OR "CABG"[Title/Abstract] OR "coronary artery bypass"[Title/Abstract] OR "valve surgery"[Title/Abstract] OR "cardiac valve"[Title/Abstract])	('acute normovolemic hemodilution':ti,ab,kw OR 'acute normovolaemic hemodilution':ti,ab,kw OR 'acute normovolemic haemodilution':ti,ab,kw OR 'acute normovolaemic haemodilution':ti,ab,kw OR 'normovolemic hemodilution':ti,ab,kw OR 'normovolaemic haemodilution':ti,ab,kw OR 'isovolemic hemodilution':ti,ab,kw OR 'isovolaemic haemodilution':ti,ab,kw) AND ('cardiac surgery':ti,ab,kw OR 'heart surgery':ti,ab,kw OR 'cardiopulmonary bypass':ti,ab,kw OR 'coronary artery bypass':ti,ab,kw OR 'valve surgery':ti,ab,kw)	(TITLE-ABS-KEY ("acute normovolemic hemodilution" OR "acute normovolaemic hemodilution" OR "acute normovolemic haemodilution" OR "acute normovolaemic haemodilution" OR "normovolemic hemodilution" OR "normovolaemic haemodilution" OR "isovolemic hemodilution" OR "isovolaemic haemodilution" OR ANH) AND TITLE-ABS-KEY ("cardiac surgery" OR "cardiac surgical" OR "heart surgery" OR "cardiopulmonary bypass" OR CPB OR CABG OR "coronary artery bypass" OR "valve surgery" OR "cardiac valve"))	#1 MeSH descriptor: [Hemodilution] explode all trees #2 ("acute normovolemic hemodilution" OR "acute normovolaemic hemodilution" OR "acute normovolemic haemodilution" OR "acute normovolaemic haemodilution" OR "normovolemic hemodilution" OR "normovolaemic haemodilution" OR "isovolemic hemodilution" OR "isovolaemic haemodilution" OR ANH):ti,ab,kw #3 ("cardiac surgery" OR "cardiac surgical" OR "heart surgery" OR "cardiopulmonary bypass" OR CPB OR CABG OR "coronary artery bypass" OR "valve surgery" OR "cardiac valve"):ti,ab,kw #4 #1 OR #2 #5 #3 #6 #4 AND #5

TABLE 3: Database-specific search strategies and number of records retrieved from PubMed, Embase, Scopus, and the Cochrane Library

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Muhammad Ayhan Amir, Shah Jahan, Ali Sanan Ahmed, Toki Babajide, Zishaan Haider Abbas, Maisha Samiha, Cathrine Nixon, Muhammad Arslan Tariq, Shamanpreet Kaur

Drafting of the manuscript: Muhammad Ayhan Amir, Zaiba Tallat, Ali Sanan Ahmed, Zishaan Haider Abbas, Cathrine Nixon, Muhammad Arslan Tariq

Critical review of the manuscript for important intellectual content: Muhammad Ayhan Amir, Zaiba Tallat, Shah Jahan, Toki Babajide, Zishaan Haider Abbas, Maisha Samiha, Cathrine Nixon, Shamanpreet Kaur

Concept and design: Zaiba Tallat, Shah Jahan, Ali Sanan Ahmed, Toki Babajide, Maisha Samiha, Muhammad Arslan Tariq, Shamanpreet Kaur

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Muhammad Ayhan Amir and Muhammad Arslan Tariq contributed equally to this manuscript and should be considered co-first authors. All identified records were added to Rayyan AI for reference management, duplicate identification, and study screening. The authors reviewed and verified the outputs of any AI-assisted features used and take full responsibility for the resulting study-selection decisions and the accuracy of the reported information.

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