CJC Open 5 (2023) 494–507

Systematic Review/Meta-Analysis

Continuous Ultrafiltration Enhances Recovery After Adult Cardiac Surgery With Cardiopulmonary Bypass: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Cardiac surgery with cardiopulmonary bypass is associated with systemic inflammation. Ultrafiltration used throughout the cardiopulmonary bypass time, continuously, is hypothesized to be an immunomodulatory therapy.

Methods: A systematic review and meta-analysis of randomized trials investigating continuous forms of ultrafiltration during adult cardiac surgery (CRD42020219309) was conducted and is reported following PRISMA guidelines. MEDLINE, Embase, CENTRAL, and Scopus were searched on November 3, 2021. The primary endpoint was operative mortality, and secondary outcomes included intensive care unit length of stay (ICU LOS), ventilation time, acute kidney injury or renal failure, and pneumonia. Each study was assessed for risk of bias using the Cochrane Risk-of Bias-Tool for Randomized Trials (RoB2) instrument. Outcomes were analyzed with inverse variance random-effects models and assessed for GRADE quality of evidence.

Results: Twelve randomized trials consisting of 989 adult patients undergoing coronary, valvular, or concomitant cardiac procedures were

RÉSUMÉ

Contexte : La chirurgie cardiaque avec pontage cardiopulmonaire est associée à une inflammation généralisée. On croit que l'ultrafiltration utilisée en continu tout au long du pontage cardiopulmonaire pourrait se révéler un traitement immunomodulateur.

Méthodologie : Une revue systématique et une métanalyse d'essais avec répartition aléatoire portant sur les formes d'ultrafiltration continue utilisées pendant une chirurgie cardiaque chez l'adulte (CRD42020219309) ont été réalisées, et les résultats sont présentés selon les lignes directrices PRISMA. Les bases de données MEDLINE, Embase, CENTRAL et Scopus ont été interrogées le 3 novembre 2021. L'étude avait pour critère d'évaluation principal la mortalité pendant la chirurgie, et pour critères secondaires, la durée du séjour aux soins intensifs, la durée de ventilation, la survenue de lésions rénales aiguës ou d'insuffisance rénale et la pneumonie. Pour chaque étude, le risque de biais a été évalué à l'aide de l'instrument Risk-of Bias-Tool for Randomized Trials (RoB2) du réseau Cochrane. Les résultats ont été analysés à l'aide de modèles à effets aléatoires selon l'inverse de la

Cardiac surgery and cardiopulmonary bypass (CPB) feature multiple proinflammatory stimuli, including surgical trauma, complement activation via exposure to non-endothelialized circuit, myocardial ischemia, and others.[1] This innate response can culminate in systemic inflammation, and endothelial leak yielding cardiopulmonary and vasomotor dysfunction, which is prohibitive to a timely postoperative recovery.[2-4] The vigorous research and development of high-quality myocardial protection techniques revolutionized the field and dramatically improved outcomes for adults undergoing cardiac surgery.[5] However, therapies that dampen the complement-mediated response to CPB have not been utilized routinely.

Ultrafiltration was developed in the early 1990s in pediatric cardiac surgery, to reduce inflammation and prevent volume overload. This therapy extracts excess water and molecules smaller than the membrane pore size, which include many proinflammatory mediators.[4] Ultrafiltration protocols can vary widely in terms of duration of use, rate of effluent removal, and volume balance targets. Noncontinuous forms of ultrafiltration, such as conventional ultrafiltration (CUF) and

Received for publication January 24, 2023. Accepted March 17, 2023.

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Review Registration: PROSPERO CRD42020219309.

See page 506 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.03.009

included. Compared to controls, patients receiving continuous ultrafiltration had no statistical difference in operative mortality; risk ratio of 0.32 (95% confidence interval [CI]: 0.10-1.03; $P = 0.06$). Reductions occurred in ICU LOS, by 7.01 hours (95% CI: 1.86-12.15; $P = 0.008$); ventilation time, by 2.11 hours (95% CI: 0.71-3.51; $P = 0.003$); and incidence of pneumonia, with a risk ratio of 0.33 (95% CI: 0.15-0.75; $P = 0.008$). There wasno difference in renal injury. The GRADE quality of evidence for these outcomes ranged from very low to low.

Conclusions: Continuous forms of ultrafiltration enhance recovery after adult cardiac surgery by reducing ICU LOS, ventilation time, and incidence of pneumonia. A multicentre randomized trial could confirm and generalize these findings.

variance, et la qualité des données a été évaluée selon l'échelle GRADE.

Résultats : Ont été incluses les données de douze essais avec répartition aléatoire auxquels ont pris part 989 patients adultes ayant subi une intervention chirurgicale coronarienne ou valvulaire, ou une chirurgie cardiaque concomitante. Le taux de mortalité enregistré pendant la chirurgie chez les patients qui avaient reçu une ultrafiltration continue ne s'est pas avéré statistiquement différent de celui relevé chez les témoins; rapport de risque = 0,32 (intervalle de confiance [IC] à 95 % : 0,10 à 1,03; $p = 0,06$). La durée du séjour aux soins intensifs a diminué de 7,01 heures (IC à 95 % : 1,86 à 12,15; $p = 0,008$), et le temps de ventilation, de 2,11 heures (IC à 95 % : 0,71 à 3,51; $p = 0,003$); l'incidence de pneumonie a également baissé (rapport de risques = 0,33 [IC à 95 % : 0,15 à 0,75; $p = 0,008$]). Aucune différence n'a été observée sur le plan des lésions rénales. La qualité des données selon l'échelle GRADE pour ces résultats allait de faible à très faible.

Conclusions : L'ultrafiltration continue améliore le rétablissement après une chirurgie cardiaque chez l'adulte en réduisant la durée du séjour aux soins intensifs, le temps de ventilation et l'incidence de pneumonie. Un essai multicentrique à répartition aléatoire pourrait confirmer et généraliser ces conclusions.

modified ultrafiltration (MUF), are used for brief periods of time at the end of the CPB time or after the patient is weaned. A reduction in bleeding complications, by hemoconcentration of blood cells and coagulation factors, has been observed in adult and pediatric populations.[4,6] Continuous forms of ultrafiltration—such as zero-balance ultrafiltration (ZBUF), subzero-balance ultrafiltration (SBUF), and dilutional ultrafiltration—are used throughout the entire CPB time.

Continuous ultrafiltration presents an opportunity to actively extract circulating proinflammatory cytokines and give precise volume balance control from the moment CPB is initiated. Theoretically, reduced inflammation and removal of excess water could translate into improved cardiopulmonary function and enhanced recovery in the postoperative period. The objective of this systematic review and meta-analysis of randomized trials is to investigate whether continuous forms of ultrafiltration yield immediate postoperative clinical benefits for adults undergoing cardiac surgery.

Methods

The protocol for this systematic review and metanalysis was previously published and registered in PROSPERO (International Prospective Register of Systematic Reviews) with identification CRD42020219309.[7] The methods are derived from the Cochrane Handbook's guidelines for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[8,9] Please see the PRISMA checklist available in Supplemental Table S1.

Search strategy and data sources

An information specialist (L.B.) designed the systematic search strategy in MEDLINE (Ovid MEDLINE All); Embase (Elsevier); the Cochrane Central Register of Controlled Trials (CENTRAL); and Scopus (Elsevier) and executed it on November 3, 2021, dated back to database inception. Key search terms included the following: "cardiopulmonary bypass"; "ultrafiltration"; "hemofiltration"; "continuous"; "dilutional"; "subzero"; "zero balance"; "modified"; and "conventional." No search filters were applied other than an English-language limit due to feasibility. The search strategy for MEDLINE, Embase, CENTRAL and Scopus are provide in Supplemental Tables S2-S5, and a summary of the systematic search is provided in Supplemental Table S6.

Study selection criteria and risk of bias

Studies were selected for inclusion if they met the following prespecified criteria: (i) had a randomized controlled trial (RCT) study design; (ii) had participants with age > 18 years undergoing cardiac surgery and CPB; (iii) had an intervention that was any type of continuous ultrafiltration used throughout the entire CPB time (CUF, ZBUF, SMUF, dilutional ultrafiltration, and combination techniques, such as ZBUF-MUF); (iv) had a comparator that was a noncontinuous form of ultrafiltration (CUF used only during rewarming or MUF) or any noninterventional control; and (v) was published in English. No exclusion was made based on patient sex, type of adult cardiac surgery, type of continuous ultrafiltration, or ultrafiltration rate.

Two reviewers (J.B. and D.H.) independently screened the titles and abstracts identified by the systematic search using Covidence.[10] Furthermore, J.B. and D.H. independently screened the full texts to identify the RCTs that meet the inclusion criteria, and the reasons for any study exclusion were recorded. The risk of bias of included studies was assessed by independent completion of the Revised Cochrane Risk-of-Bias (RoB2) tool by J.B. and D.H.[11] A third reviewer (R.S.) was available to arbitrate any disagreement in the study selection or risk-of-bias assessment processes.

Study method, demographics, and outcomes

J.B. and D.H. independently extracted prespecified information about the included studies regarding methods, patient demographics, and outcomes. Information extracted on study methods included the following: the authors; publication date; randomization design; trial start and end date; and treatment (including specifics on the type of continuous ultrafiltration and total effluent volume) and control arms, as well as the number of patients in each arm. Patient demographic information extracted included the following: sex; mean age; surgical risk (low risk defined as Society of Thoracic Surgery (STS) or European System for Cardiac Operative Risk Evaluation (EuroSCORE) II mortality risk score < 4; moderate or high risk defined as either score > 4 or the presence of severe medical comorbidity or organ dysfunction); type of cardiac surgery (CPB surgery, valvular surgery, concomitant coronary-valve surgery, and aortic surgery); CPB time; and aortic cross-clamp time.

The prespecified primary outcome was operative mortality (death during the same hospitalization as the cardiac operation or within 30 days of the operation). Prespecified secondary outcomes were as follows: invasive ventilation time; intensive care unit length of stay (ICU LOS); incidence of acute kidney injury (AKI) or renal failure; stroke; bleeding complications; sternal wound infection; pneumonia; and patient-reported outcomes on postoperative recovery. Missing data were not imputed.

Statistical analysis

J.B. and D.H. independently extracted data from included studies, cross-referenced for accuracy, and imported them into Review Manager version 5.3 (RevMan) for analysis.[12] Dichotomous outcomes were analyzed by the inverse variance random-effects method, and were expressed as risk ratios with 95% confidence intervals (CIs). Continuous outcomes were also analyzed by an inverse variance random-effects method, and were expressed as mean difference with 95% CIs. A random-effects model was used because of the suspected heterogeneity in types of continuous ultrafiltration methods used, underlying cardiac pathology, and patient risk profile. A meta-analysis was performed only if at least 2 included studies reported the same outcome. As stated in the prespecified protocol, any statistically significant difference in the primary and key secondary outcomes was deemed clinically relevant.

Statistical heterogeneity was measured by the χ^2 test (with $P < 0.1$ indicating significant heterogeneity) and was described by the I^2 statistic. $I^2 > 75\%$ suggests substantial heterogeneity, and outcomes that exhibit this pattern underwent investigation to better understand the root causes of the heterogeneity between studies. Reporting bias examination by a funnel plot analysis was completed if 10 or more studies reported on an outcome. One prespecified subgroup analysis was completed that differentiated patients by operative risk profile, as follows: low risk (STS or EuroSCORE II mortality risk score < 4) vs moderate or high risk (STS or EuroSCORE II mortality risk score > 4 or the presence of severe medical comorbidity or organ dysfunction). Examples of preoperative organ dysfunction include renal, cardiac, pulmonary, and hepatic failure. Test for subgroup interactions was completed using RevMan.[12]

A sensitivity analysis evaluated the meta-analysis results. Studies that were judged to have a high risk of bias, via the Cochrane RoB2 tool, were excluded from the pooled analysis for comparison with the primary results.

Quality of evidence

The quality of included evidence was characterized, independently by J.B. and D.H., through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[13] Domains that determine the certainty of result through the GRADE system include the following: risk of bias; inconsistency of outcome results; indirectness of results; imprecision of results; suspicion of publication bias; effect size; plausible confounding; and dose-response gradient.[13]

Results

Study selection and inclusion

The study selection process is illustrated by the PRISMA consort diagram in Figure 1. A total of 646 abstracts and 20 full-text articles were assessed for eligibility, yielding 12 RCTs, consisting of 989 patients, that were included in the meta-analysis (Table 1).[14-25] A large range was found in study publication dates (1997-2020); types of continuous ultrafiltration used in the intervention arm (CUF, ZBUF, SBUF, CUF-MUF); and types of cardiac intervention (coronary artery bypass grafting, valvular, concomitant coronary artery bypass grafting-valve, and aortic surgery). The intraoperative data from included studies are reported in Table 2. Mean CPB time ranged between 64 and 182 minutes, and mean cross-clamp time ranged between 32 and 145 minutes. Most studies reported the continuous ultrafiltration target, which featured widely varying protocols, whereas only half reported the total ultrafiltrate effluent volume, which again differed among trials (Table 2).

The majority of studies consisted of patients judged to have low operative risk, whereas only 3 recent trials—Matata et al.[23] (2015), Plotnikov et al.[24] (2019), and Garcia-Camacho et al.[25] (2020)—were deemed to have patients at moderate or high operative risk. More recently published studies directly reported EuroSCORE or EuroSCORE II characteristics of included patients, whereas older studies did not (Table 1). All studies had a single-centre design and lacked important methods, such as sample size calculations and prespecified study design and analysis. Reporting of post-operative outcomes of interest was inconsistent, and a summary can be seen in Supplemental Table S7. One study was judged to have a low risk of bias; 4 were judged to have moderate concerns regarding risk of bias; and 7 studies were judged to be at high risk of bias. Individual assessments of biases can be visualized based on Table 3. The construction of funnel plots was deferred, as no outcome was reported by 10 or more studies.

Operative mortality

Four of the 12 included studies directly reported operative mortality, on 502 patients (Fig. 2). Overall, this outcome was

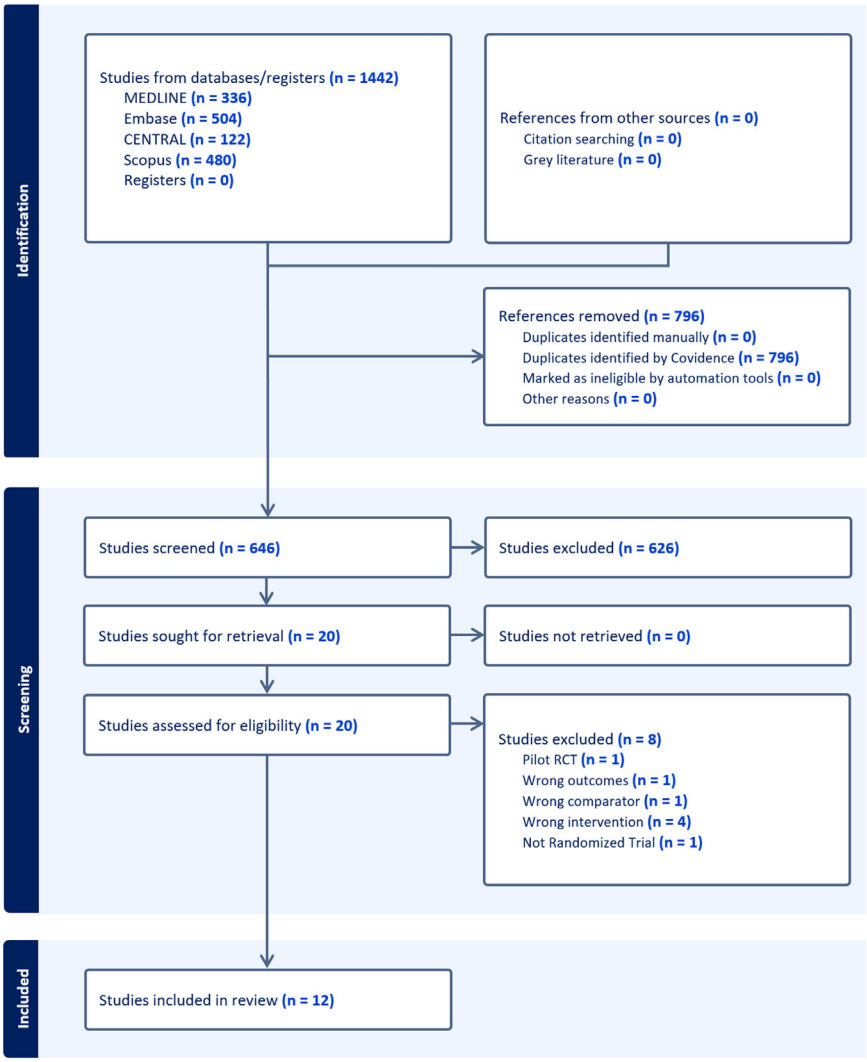

Figure 1. Consort flow diagram. CENTRAL, Cochrane Central Register of Controlled Trials; RCT, randomized controlled trial.

rare and was observed in 1.2% of the patients receiving ultrafiltration and 4.5% of the patients in the control groups; number needed to treat = 30. The pooled analysis revealed a reduced risk of mortality with ultrafiltration, by a risk ratio of 0.32 (95% CI: 0.10-1.03) that did not reach statistical significance ($P = 0.06$). Consistency of effect between both risk subgroups was present, and these results were heavily influenced by the study by Matata et al.,[23] which contributed 86.4% of the analysis weight. The pooled analysis showed very low levels of heterogeneity ($I^2 = 0\%$). A prespecified sensitivity analysis (Supplemental Fig. S1) was conducted by removing Santarpino et al.[19] and Zhang et al.[20], which were at high risk of bias, yielding a similar effect size with a more imprecise risk ratio of 0.32 (95% CI: 0.09-1.11), which considers only results from Matata et al.[23]

Intensive care unit length of stay

Eight of the 12 included studies directly report ICU LOS (hours), on 595 patients (Fig. 3). A significant mean reduction occurred in ICU LOS, of 7.01 hours (95% CI: 1.86-12.15; $P = 0.008$), for patients receiving ultrafiltration, compared to that of controls. This difference represents a 13% reduction in ICU LOS from the 55.65 hours weighted average recorded in control patients. Both the low-risk and moderate- or high-risk subgroups showed a reduction in ICU LOS, but the moderate- or high-risk subgroup showed a significantly larger effect size ($P = 0.02$). A moderate degree of heterogeneity was observed in the low-risk subgroup ($I^2 = 73\%$); a low degree was observed in the moderate- or high-risk subgroup ($I^2 = 12\%$); and a high degree was observed in the combined analysis ($I^2 = 79\%$). A prespecified sensitivity analysis (Supplemental Fig. S2) was conducted by removing de Baar et al.,[16] Zhang et al.,[20,21] Plotnikov et al.,[24] and Garcia-Camacho et al.[25] as studies with high risk of bias. The resulting sensitivity analysis included only low-risk subgroup studies, and the benefit of ultrafiltration on ICU LOS was neutralized with a reduction of 3.99 hours (95% CI: -3.88-11.85).

Invasive ventilation time

Nine of the 12 included studies directly report ventilation time (hours), on 794 patients (Fig. 4). Matata et al.[23] reported this outcome as median and interquartile range, which was

Table 1. Patient characteristics of included studies

Study	n	Operation Type (%)	Key Characteristics	Intervention Control	Age (year)	Male (%)	Operative Risk Score	Operative Risk Class
Babka et al.[14] (1997)	60	CABG (100)	NR	**CUF** No UF	63 ± 9.5 59 ± 10.8	70 78	NR NR	Low Low
Tallman et al.[15] (2002)	31	CABG (97) Valvular (3)	Excluded severe comorbidities	**ZBUF** No UF	62.7 ± 9.5 62.8 ± 7.3	80 67	NR NR	Low Low
de Baar et al.[16] (2003)	60	CABG (100)	Elective	**ZBUF** No UF	67 ± 8 66 ± 9	79 74	NR NR	Low Low
Kuntz et al.[17] (2006)	100	CABG (NR) Valvular (NR)	Excluded renal insufficiency	**CUF** No UF	63 ± 12 64 ± 10	79 74	NR NR	Low Low
Luciani et al.[18] (2009)	40	CABG (100)	Excluded severe comorbidities	**SBUF** No UF	66.1 ± 11.1 65.2 ± 8.4	NR NR	NR NR	Low Low
Santarpino et al.[19] (2009)	24	CABG (100)	Elective, excluded LVEF < 40%, redo surgery, recent MI and severe comorbidities	**CUF** Steroids*	63.3 ± 9.2 59.3 ± 10.1	75 75	ASA score: 3.1 ± 1.6 ASA score 2.8 ± 1.1	Low Low
Zhang et al.[20] (2009)	120	CABG (33) Valvular (58) Concomitant (5) VSD or ASD repair (4)	Excluded renal insufficiency	**SBUF** No UF	60.7 ± 11.5 62.9 ± 13.2	63 68	NR NR	Low Low
Zhang et al.[21] (2011)	94	Valvular (95) Concomitant (5)	Excluded renal insufficiency	**SBUF** No UF	61.5 ± 12.6 63.8 ± 11.8	55 64	NR NR	Low Low
Foroughi et al.[22] (2014)	159	CABG (84) Valvular (16)	Elective, excluded renal insufficiency	**CUF-MUF** No UF	57 ± 12 57 ± 11	60 71	EuroSCORE: 2.6 ± 1.4 EuroSCORE: 2.4 ± 1.5	Low Low
Matata et al.[23] (2015)	199	CABG (31) Valvular (42) Concomitant (27)	Included renal insufficiency eGFR = 15−60 mL/min	**ZBUF** No UF	73.3 ± 9.5 70.5 ± 10.4	59 60	EuroSCORE: 7.8 ± 2.9 EuroSCORE: 7.3 ± 3.2	Moderate−High Moderate−High
Plotnikov et al.[24] (2019)	38	Concomitant (100)	Excluded urgent operations	**ZBUF** No UF	72.1 ± 12.7 69.3 ± 11.3	100 100	EuroSCORE 2: 4.3 EuroSCORE 2: 3.7	Moderate−High Moderate−High
Garcia-Camacho et al.[25] (2020)	64	CABG (14) Valvular (69) Concomitant (9) Aortic (8)	Excluded urgent operations and renal insufficiency	**ZBUF** No UF	63.8 ± 10.8 62.8 ± 11.6	56 78	EuroSCORE: 5.0 ± 1.9 EuroSCORE: 5.0 ± 1.8	Moderate−High Moderate−High

Age is given as mean ± standard deviation.

ASA, American Society of Anesthesiology; ASD, atrial septal defect; CABG, coronary artery bypass grafting; CUF, conventional ultrafiltration; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MUF, modified ultrafiltration; NR, not recorded; SBUF, subzero-balance ultrafiltration; UF, ultrafiltration; VSD, ventricular septal defect; ZBUF, zero-balance ultrafiltration.

*Steroids were methylprednisolone 15 mL/kg at anesthesia induction.

converted to median and standard deviation for analysis with methods previously described.[26,27] A mean reduction (95% CI) of 2.11 hours (95% CI: 0.71-3.51) ($P = 0.003$) was seen for patients receiving ultrafiltration, compared to controls. This difference represents an 18% reduction in ventilation time from the 11.51 hours weighted average observed in the control group. Both the low-risk and moderate- or high-risk subgroups showed similar effect estimates. A very high

Table 2. Operative characteristics of included studies

Study	n	Operation Type (%)	UF Target	Intervention Control	CPB Time (min)	CX Time (min)	Effluent Volume (mL)
Babka et al.[14] (1997)	60	CABG (100)	NR	**CUF** No UF	64 ± 21 73 ± 21	32 ± 12 38 ± 15	NR 0
Tallman et al.[15] (2002)	31	CABG (97) Valvular (3)	3.0 L / m^2	**ZBUF** No UF	NR NR	NR NR	6472 0
de Baar et al.[16] (2003)	60	CABG (100)	40 mL/min per m^2	**ZBUF** No UF	112 ± 34 116 ± 36	85 ± 26 86 ± 25	NR 0
Kuntz et al.[17] (2006)	100	CABG (NR) Valvular (NR)	> 400 mL/15 min	**CUF** No UF	103 ± 51 96 ± 36	69 ± 32 65 ± 23	5871 ± 2612 0
Luciani et al.[18] (2009)	40	CABG (100)	35 mL/kg per h	**SBUF** No UF	112 ± 33 110 ± 29	64 ± 24 63 ± 23	NR 0
Santarpino et al.[19] (2009)	24	CABG (100)	NR	**CUF** Steroids*	71 ± 11 85 ± 22	56 ± 8 67 ± 16	NR 0
Zhang et al.[20] (2009)	120	CABG (33) Valvular (58) Concomitant (5) VSD /ASD Repair (4)	10−100 mL/kg	**SBUF** No UF	120 ± 41 117 ± 47	83 ± 27 80 ± 29	3532 ± 1669 0
Zhang et al.[21] (2011)	94	Valvular (95) Concomitant (5)	10−100 mL/kg	**SBUF** No UF	101 ± 36 93 ± 35	68 ± 17 62 ± 20	3159 ± 940 0
Foroughi et al.[22] (2014)	159	CABG (84) Valvular (16)	25−30 mL/kg	**CUF-MUF** No UF	102 ± 32 108 ± 27	66 ± 24 66 ± 16	2310 ± 880 0
Matata et al.[23] (2015)	199	CABG (31) Valvular (42) Concomitant (27)	> 100 mL/min	**ZBUF** No UF	110 ± 18 109 ± 16	76 ± 12 80 ± 14	8625 ± 2475 0
Plotnikov et al.[24] (2019)	38	Concomitant (100)	80 mL/min	**ZBUF** No UF	176 ± 52 182 ± 44	142 ± 39 145 ± 27	NR 0
Garcia-Camacho et al.[25] (2020)	64	CABG (14) Valvular (69) Concomitant (9) Aortic (8)	80 mL/kg per h	**ZBUF** No UF	96 ± 37 104 ± 52	79 ± 33 84 ± 40	NR 0

Values for CPB time and CX time are mean ± standard deviation.

ASD, atrial septal defect; CABG: coronary artery bypass grafting; CPB, cardiopulmonary bypass; CUF: conventional ultrafiltration; CX, cross-clamp; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MUF, modified ultrafiltration; NR, not recorded; SBUF, subzero-balance ultrafiltration; UF, ultrafiltration; VSD, ventricular septal defect; ZBUF, zero-balance ultrafiltration.

*Steroids were methylprednisolone 15 mL/kg at anesthesia induction.

degree of heterogeneity was observed in the low-risk subgroup (I^2 = 90%), in the moderate- or high-risk subgroup (I^2 = 96%), and in the combined analysis (I^2 = 92%). A prespecified sensitivity analysis (Supplemental Fig. S3) was conducted by removing de Baar et al.,[16] Zhang et al.,[20,21] Plotnikov et al. 2019[24] and Garcia-Camacho et al.[25] as studies with a high risk of bias. The benefit of ultrafiltration was neutralized, with an insignificant increase in ventilation time of 0.30 hours (95% CI: -2.09-2.70.

Acute kidney injury or renal failure

Seven of the 12 included studies directly reported AKI or renal failure requiring dialysis, on 654 patients (Fig. 5). Babka et al.,[14] Santarpino et al.[19], Zhang et al.,[20] and Foroughi et al.[22] reported AKI without dialysis; all were in the low-risk subgroup. Matata et al.[23] and Plotnikov et al.[24] reported renal failure requiring dialysis, whereas Garcia-Camacho et al.[25] reported renal failure without specifying the need for dialysis. No difference was present between the ultrafiltration and

Table 3. Risk of bias assessment

Study	Domain 1: randomization process	Domain 2: deviation from assigned intervention	Domain 3: missing data	Domain 4: outcome measurement	Domain 5: selection of reported result	Overall risk of bias
Babka et al.[14] (1997)	Concerns*	Low risk	Low risk	High risk†	Concerns‡	High risk
Tallman et al.[15] (2002)	Low risk	Low risk	Low risk	Low risk	Concerns‡	Concerns
de Baar et al.[16] (2003)	Low risk	Low risk	Low risk	High risk†	Concerns‡	High risk
Kuntz et al.[17] (2006)	Low risk	Low risk	Low risk	Low risk	Concerns‡	Concerns
Luciani et al.[18] (2009)	Low risk	Low risk	Low risk	Low risk	Concerns‡	Concerns
Santarpino et al.[19] (2009)	Low risk	Low risk	Low risk	High risk†	Concerns‡	High risk
Zhang et al.[20] (2009)	Low risk	Low risk	Low risk	High risk†	Concerns‡	High risk
Zhang et al.[21] (2011)	Low risk	Low risk	Low risk	High risk†	Concerns‡	High risk
Foroughi et al.[22] (2014)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Matata et al.[23] (2015)	Low risk	Low risk	Low risk	Low risk	Concerns‡	Concerns
Plotnikov et al.[24] (2019)	Low risk	Low risk	Low risk	High risk†	Concerns‡	High risk
Garcia-Camacho et al.[25] (2020)	Low risk	High risk§	High risk‖	Low risk	Concerns‡	High risk

* Unbalanced groups after randomization.
† No blinding.
‡ No prespecified analysis or reporting plan.
§ Multiple patients received different therapies than assigned, due to clinical criteria.
‖ Multiple patients excluded from analysis after randomization.

control groups, with a risk ratio of 0.84 (95% CI: 0.48-1.48). Renal injury was infrequent in the low-risk subgroup, at 4.1%, but it was more considerable in the moderate- or high-risk subgroup, at 40%, driven largely by the results of the Matata et al.,[23] study, which enrolled patients with considerable preoperative renal insufficiency, indicated by an estimated glomerular filtration rate of 15-60 mL/min.

The comparison within the low-risk subgroup had a largely imprecise risk ratio of 1.56 (95% CI: 0.43-5.68); the moderate- or high-risk subgroup showed a decreased risk of renal failure with ultrafiltration of 0.70 (95% CI: 0.36-1.34), which did not reach statistical significance. A low degree of heterogeneity was observed in the low-risk subgroup ($I^2 = 11\%$), in the moderate- or high-risk subgroup ($I^2 = 25\%$), and in the

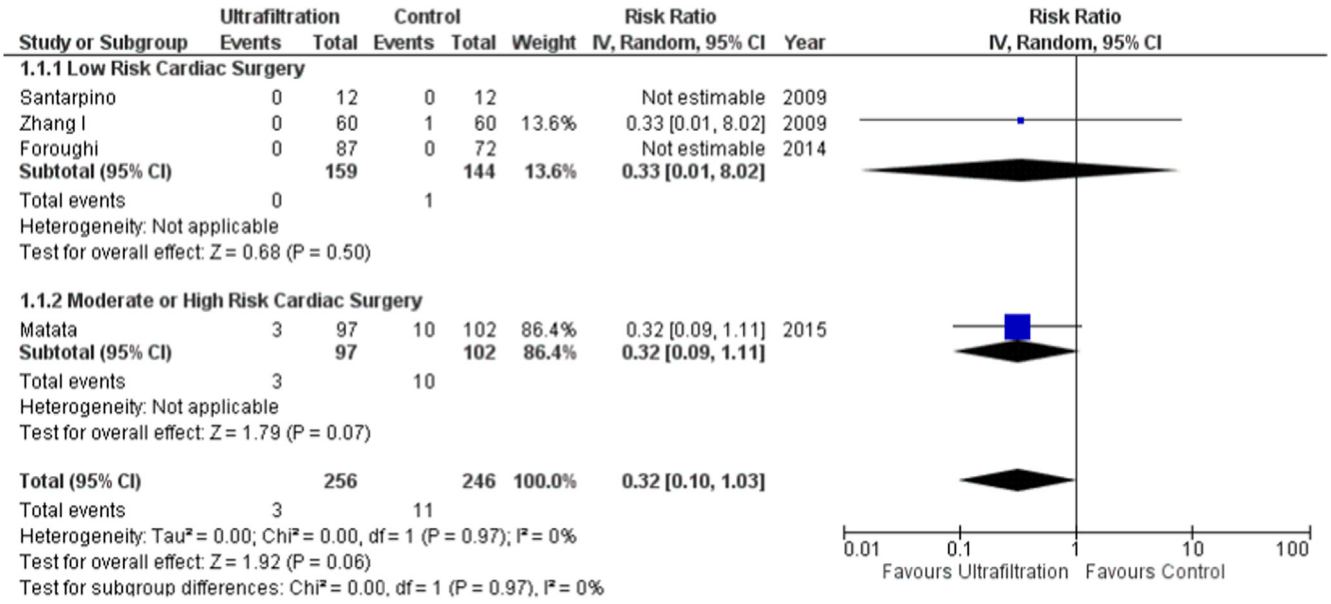

Figure 2. Operative mortality forest plot. Comparison of operative mortality events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

combined analysis (I^2 = 25%). A prespecified sensitivity analysis (Supplemental Fig. S4) was conducted by removing Babka et al.,[14] Santarpino et al.,[19] Zhang et al.,[20] Plotnikov et al.,[24] and Garcia-Camacho et al.,[25] as studies with a high risk of bias. This analysis confirmed that no difference was present between ultrafiltration and control, with a risk ratio of 0.95 (95% CI: 0.58-1.55).

Pneumonia

Four of the 12 included studies directly reported pneumonia, on 437 patients (Fig. 6). This outcome was rare and was observed in 2.8% of the patients receiving ultrafiltration and 9.6% of the patients in the control groups; number needed to treat = 15. A substantial reduction occurred, with ultrafiltration yielding a risk ratio of 0.33 (95% CI: 0.15-0.75; P = 0.008). This finding was consistent across the low-risk and moderate- or high-risk subgroups. A very low degree of heterogeneity was observed in the low-risk subgroup (I^2 = 0%) and the combined analysis (I^2 = 0%). No indication for a sensitivity analysis was present.

Chest tube bleeding

Five of the 12 included studies directly reported chest tube output (mL), on 520 patients (Fig. 7). There was a mean reduction with ultrafiltration of 44.03 mL (95% CI: 4.21-83.85), compared to control (P = 0.03). This difference represents a minor 8% reduction in the measure of total chest tube output of the 525.92 mL weighted average observed in control patients. A larger degree of bleeding reduction occurred with ultrafiltration in the low-risk subgroup,

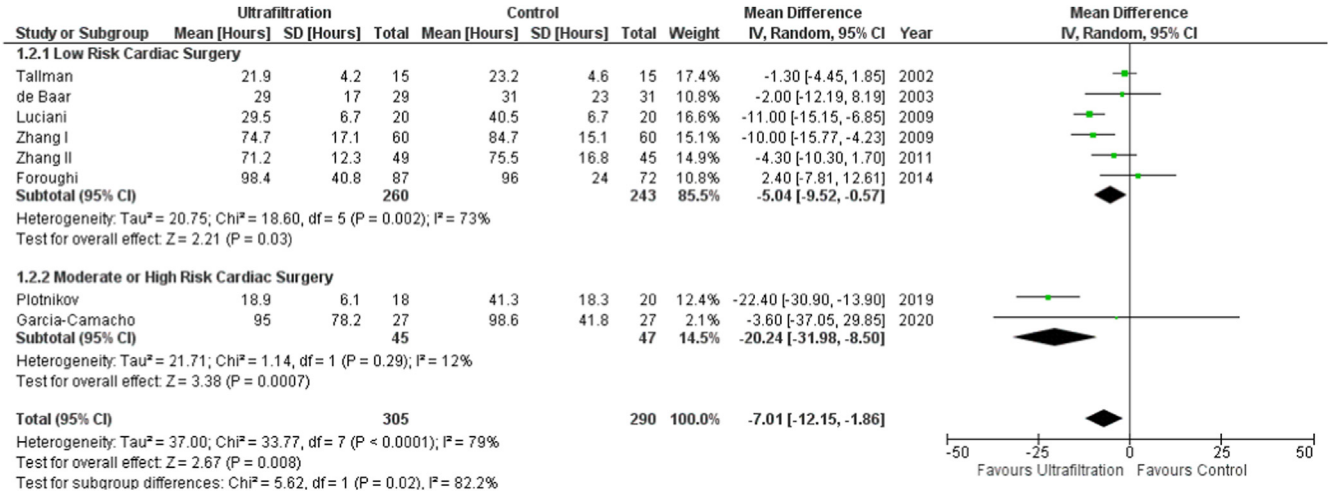

Figure 3. Intensive care unit length of stay forest plot (ICU LOS). Mean difference comparison of ICU LOS in hours between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom; SD, standard deviation.

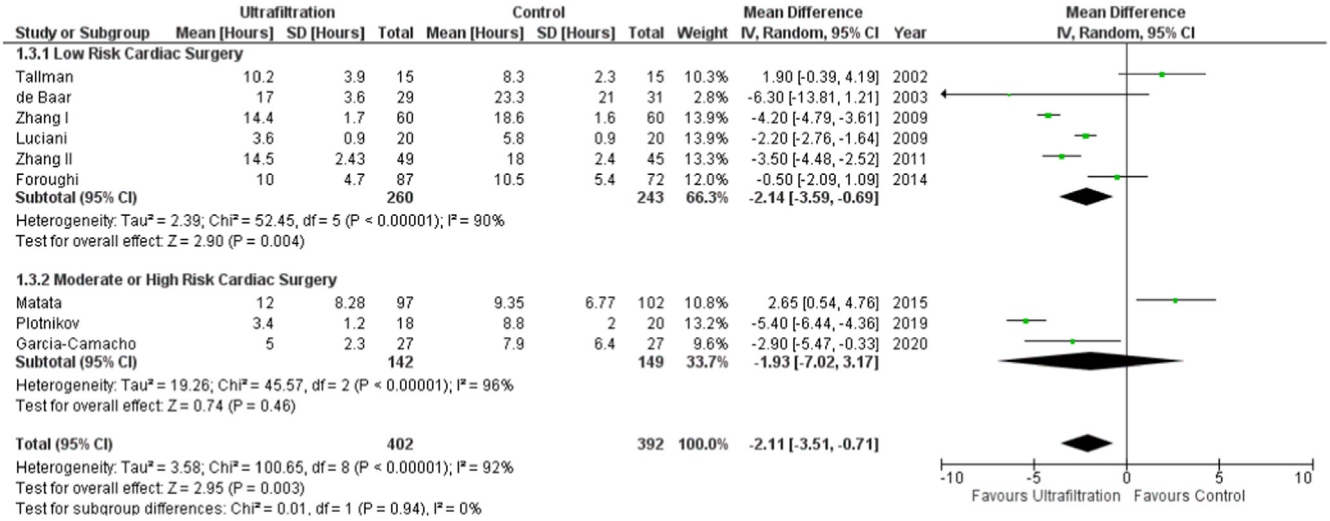

Figure 4. Mechanical ventilation time forest plot. Mean difference comparison of ventilation time in hours between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

compared to the moderate- or high-risk subgroup ($P = 0.04$). A low degree of heterogeneity was observed in the low-risk subgroup ($I^2 = 0\%$) and the moderate- or high-risk subgroup ($I^2 = 3\%$), whereas the combined analysis showed a moderate level of heterogeneity ($I^2 = 31\%$). A prespecified sensitivity analysis (Supplemental Fig. S5) was conducted by removing Zhang et al.[21] and Plotnikov et al.[24], with had a high risk of bias. The combined sensitivity analysis yielded a mean reduction in the ultrafiltration group of 71.53 mL (95% CI: -41.34-184.40) that did not reach statistical significance. The low-risk subgroup maintained a significant bleeding reduction of 150.60 mL (95% CI: 14.91-286.30) in the ultrafiltration group, compared to controls, and Matata et al.,[23] in the moderate- or high-risk subgroup, yielded a non-statistically significant mean reduction of 10.00 mL (95% CI: -33.18-53.18) with ultrafiltration.

Red blood cell transfusion

Only 4 of the 12 included studies directly reported RBC transfusion (units/patient), on 304 patients (Fig. 8). A mean reduction with ultrafiltration of 0.81 (95% CI: -0.36-

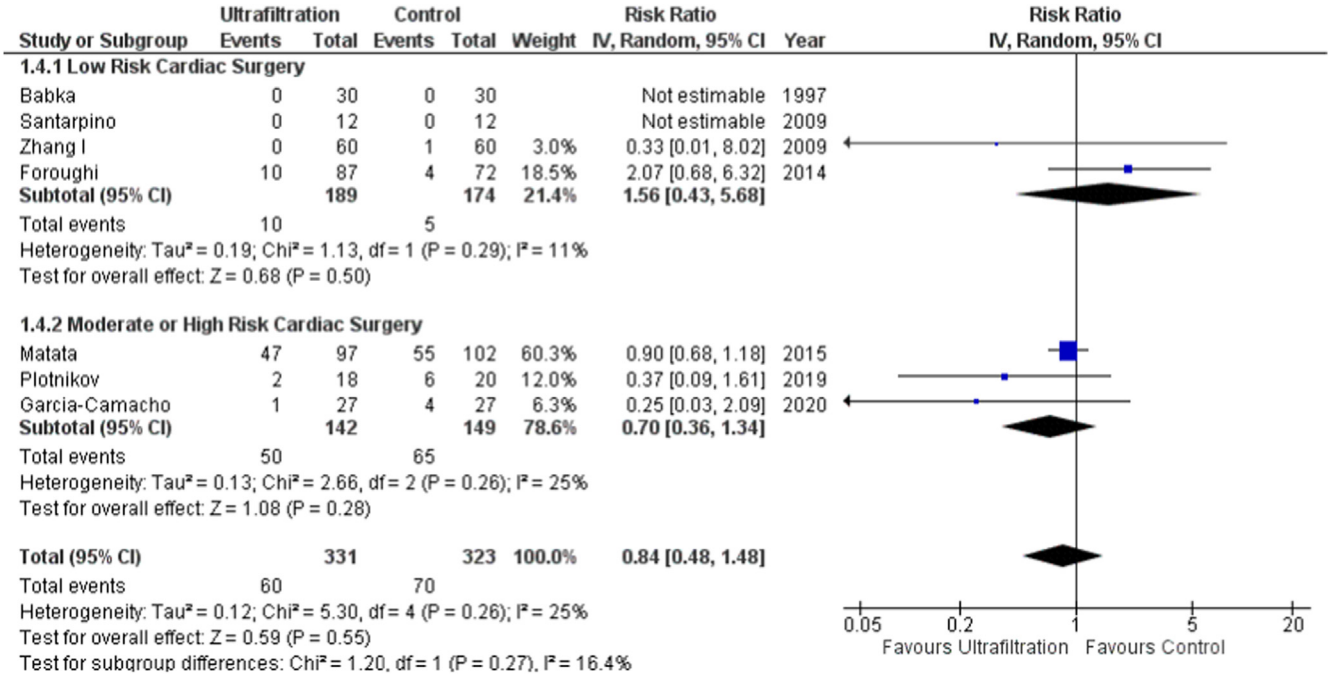

Figure 5. Acute kidney injury (AKI) or renal failure forest plot. Comparison of AKI or renal failure events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

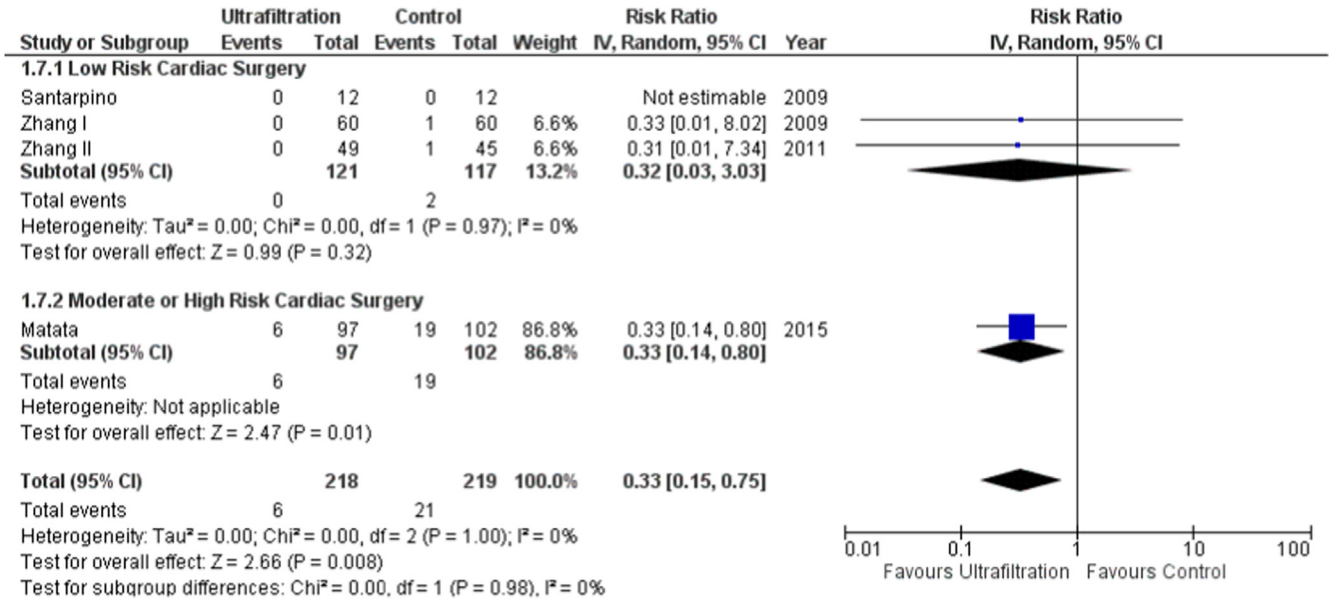

Figure 6. Pneumonia forest plot. Comparison of postoperative pneumonia events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

1.98) units/patient, compared to controls, did not reach statistical significance ($P = 0.17$). No subgroup analysis was performed, as all included studies were in the low-risk group. An exceedingly high degree of heterogeneity was observed ($I^2 = 93\%$). A sensitivity analysis was not completed, as all 4 studies were judged to be at high risk of bias.

Sternal wound infection or mediastinitis

Only 2 of the 12 included studies directly reported sternal wound infection or mediastinitis on 319 patients (Fig. 9). This outcome was rare and was observed in 0.6% of the patients receiving ultrafiltration, and 2.4% of the patients in the control groups. Zhang et al.[20] reported sternal wound complications, and Matata et al.[23] reported mediastinitis. No difference was present between the ultrafiltration and control groups, with a risk ratio of 0.34 (95% CI: 0.05-2.18). No subgroup analysis was performed, as all included studies were in the low-risk group. A very low degree of heterogeneity was observed ($I^2 = 0\%$). No indication for a sensitivity analysis was present.

Stroke

Stroke was infrequently reported and exceedingly rare. Only one such event occurred in 220 patients over 3 studies. This event occurred in the control arm of Zhang et al.[20]

Quality of evidence

The quality of evidence for the reported outcomes can be viewed in Table 4. The quality of evidence was judged to be very low or low for all outcomes. The majority of studies were

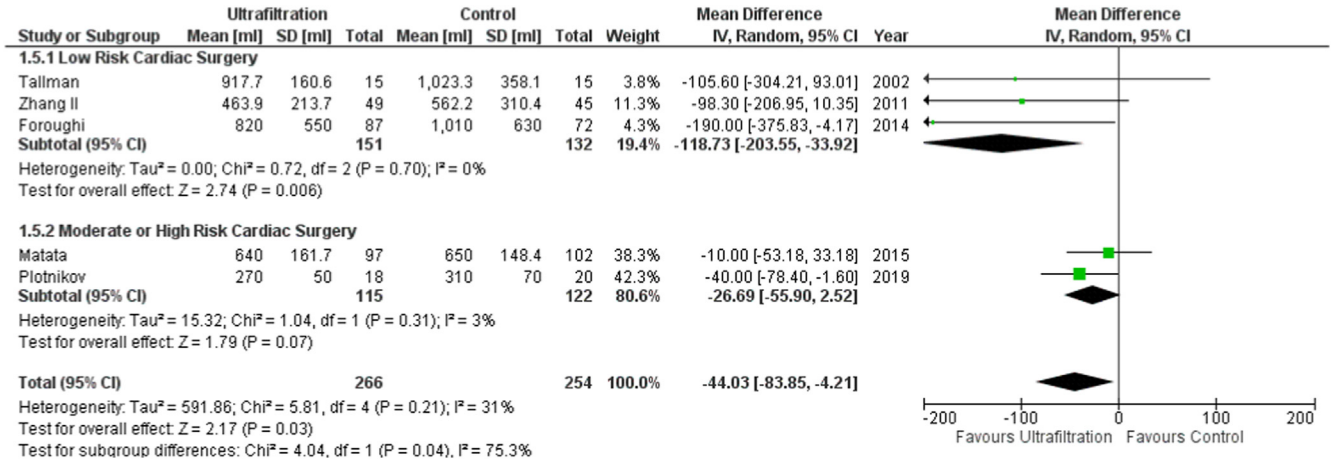

Figure 7. Total chest tube output forest plot. Mean difference comparison of chest tube output in milliliters between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

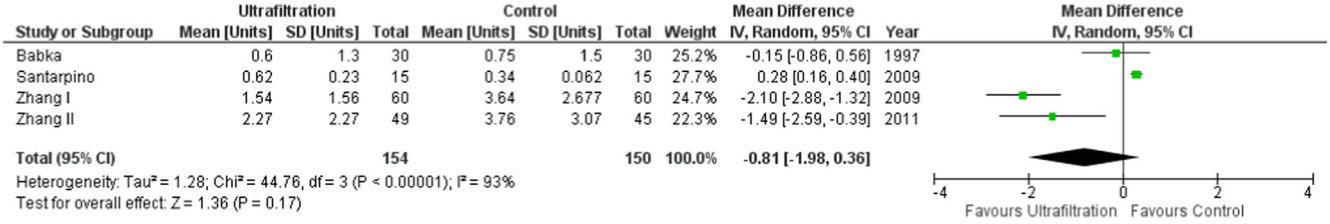

Figure 8. Red blood cell (RBC) transfusion forest plot. Mean difference comparison of RBC transfusion in units/patient between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom; SD, standard deviation.

judged to be at high risk for bias; a particular outcome was judged to be at serious risk of bias if more than half of the analyzed studies were at high risk of bias. Imprecision commonly downgraded the quality ratings for dichotomous outcomes, as CIs were generally quite large and often included the null value; these studies lack power to assess rare outcomes. Heterogeneity of patients, cardiac operations, and ultrafiltration protocols contributed to serious indirectness (differences in patient populations and interventions included in the analysis that reduce the confidence in the direct effect measure of intervention on outcome) in ICU LOS, ventilation time, AKI or renal failure, total chest tube output, and pneumonia. Furthermore, inconsistency of results among studies was a serious issue for ventilation time, AKI or renal failure, and RBC transfusion. Publication bias was generally suspected, given the selective reporting of outcomes observed among studies; the quality of evidence was downgraded if less than 75% of all included studies reported the outcome. Operative mortality and pneumonia benefited from a strong association favouring ultrafiltration.

Discussion

This systematic review and meta-analysis of RCTs is the first to investigate the clinical outcomes of continuous ultrafiltration during adult cardiac surgery with CPB. The principal finding of this study is that continuous ultrafiltration had lower relative risk of operative mortality, with a point estimate of 0.32 and 95% CI that is not statistically significant as mortality was a rare event in the included studies. The effect size was considerable, with a 3.3% absolute rate reduction and a number needed to treat of 30. The result was heavily weighted from the study by Matata et al.,[23] which enrolled moderate and high-risk patients with preoperative renal insufficiency. Although an important signal, the GRADE quality of evidence for operative mortality is very low due to risk of bias, imprecision, indirectness, and selective publication of outcomes. Furthermore, the mechanism of decreased mortality is not immediately obvious. Hypothetically, prevention of low cardiac output syndrome, critical pulmonary dysfunction, or severe vasoplegia could partially explain this finding.

Continuous forms of ultrafiltration also showed a significant reduction in ICU LOS, by 13%, which is clinically relevant. Dampening of systemic inflammation and enhancement of cardiopulmonary function could explain this consistent finding. The effect size was 4 times larger in the moderate- or high-risk subgroup (20.24-hour reduction) than it was in the low-risk subgroup (5.04-hour reduction), suggesting that vulnerable patients at high operative risk might receive more benefit from continuous ultrafiltration. The substantial amount of heterogeneity in this outcome can be well explained by differences in surgical risk, surgical procedure, ultrafiltration protocol, measurement of ICU LOS, institutional ICU practices, and year of study. The GRADE quality of evidence for ICU LOS was low, due to risk of bias and indirectness.

In synchrony with the ICU LOS results, continuous ultrafiltration had a clinicallysignificant 18% reduction in ventilation time, compared to controls. Unfortunately, the burden of heterogeneity was extreme through all parts of this outcome analysis, with similar rationale as the heterogeneity found in ICU LOS. Furthermore, data from Matata et al.[23] were converted from median and interquartile range to be included in the analysis, adding another source of potential bias. Excluding this study would not be appropriate as it is a larger trial that benefited from a higher degree of methodological rigor relative to other included studies. The GRADE quality of evidence was low due to inconsistency and indirectness.

Continuous ultrafiltration has several therapeutic mechanisms that support postoperative recovery by ameliorating the noxious responses to CPB-associated inflammation, with a breadth of evidence from pediatric cardiac surgery experience.[1,3,4] First, it extracts proinflammatory mediators during

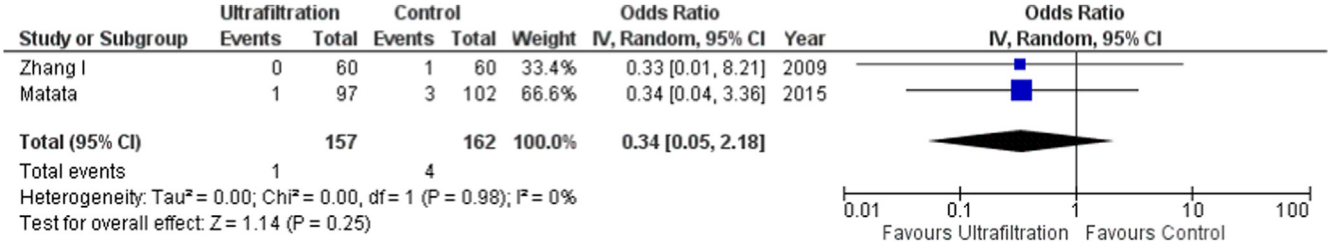

Figure 9. Sternal wound infection forest plot. Comparison of postoperative sternal wound infection events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

Table 4. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) certainty of evidence and summary of findings

Participants (# RCTs)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With continuous ultrafiltration		Risk with control	Risk difference with continuous ultrafiltration
Operative Mortality											
502 (4)	Serious‖	Not serious	Serious*	Serious†	Publication bias strongly suspected‡	⨁◯◯◯ **Very low**	11/246 (4.5)	3/256 (1.2)	**RR 0.32** (0.10 to 1.03)	4 per 100	**3 fewer per 100** (from 4 fewer to 0 fewer)
Intensive Care Unit Length of Stay											
595 (8)	Serious‖	Not serious	Serious*	Not serious	None	⨁⨁◯◯ **Low**	—	—	—	—	MD **7.01 h lower** (12.15 lower to 1.86 lower)
Invasive Ventilation Time											
794 (9)	Not serious	Serious§	Serious*	Not serious	None	⨁⨁◯◯ **Low**	—	—	—	—	MD **2.11 h lower** (3.51 lower to 0.71 lower)
Acute Kidney Injury or Renal Failure											
654 (7)	Serious‖	Serious§	Very serious*	Serious†	Publication bias strongly suspected‡	⨁◯◯◯ **Very low**	70/323 (21.7)	60/331 (18.1)	**RR 0.84** (0.48 to 1.48)	22 per 100	**3 fewer per 100** (from 11 fewer to 7 more)
Pneumonia											
437 (4)	Serious‖	Not serious	Serious*	Not serious	Publication bias strongly suspected‡	⨁⨁◯◯ **Low**	21/219 (9.6)	6/218 (2.8)	**RR 0.33** (0.15 to 0.75)	10 per 100	**6 fewer per 100** (from 8 fewer to 2 fewer)
Total Chest Tube Output											
520 (5)	Not serious	Not serious	Serious*	Not serious	Publication bias strongly suspected‡	⨁⨁◯◯ **Low**	—	—	—	—	MD **44.03 ml lower** (83.85 lower to 4.21 lower)
Red Blood Cell Transfusion											
244 (3)	Serious‖	Serious§	Not serious	Serious†	Publication bias strongly suspected‡	⨁◯◯◯ **Very low**	—	—	—	—	MD **1.06 units/ patient lower** (2.83 lower to 0.7 higher)
Sternal Wound Infection											
319 (2)	Serious‖	Not serious	Not serious	Very serious¶	Publication bias strongly suspected‡	⨁◯◯◯ **Very low**	4/162 (2.5)	1/157 (0.6)	**RR 0.34** (0.05 to 2.18)	2 per 100	**2 fewer per 100** (from 2 fewer to 3 more)

CI, confidence interval; MD, mean difference; RCT, randomized controlled trial; RR: risk ratio.
* Differences in surgical population and procedures.
† 95% CI includes null.
‡ Selective reporting of outcomes between included studies.
§ Opposite polarity of effect between studies.
‖ More than half of analyzed studies show high risk of bias.
¶ 95% CI is considerably wide.

the entire CPB time, which is a potent stimulant for complement system activation. Reduction in systemic inflammation should translate into improved cardiopulmonary function, vasomotor integrity, and medical stability in the postoperative period. Second, by targeting a slight negative volume balance through the ultrafiltration protocol, volume overload is avoided. This approach potentially prevents myocardial and pulmonary edema, which facilitates a timely weaning and separation from mechanical ventilation.[4] Third, balanced ultrafiltration protocols infuse buffered physiologic solutions that maintain normal acid-base parameters in the intra- and postoperative period. Importantly, this therapy poses very little risk to the patient and is easy to implement by an experienced perfusion team.

Ultrafiltration during adult cardiac surgery has been postulated to cause AKI in retrospective cohort analysis, particularly when ultrafiltration volumes are above 32 mL/kg.[28] A recent systematic review and meta-analysis of adult cardiac surgery randomized trials directly investigating AKI, including subgroup analysis of noncontinuous ultrafiltration (ie, MUF) as well as continuous forms (ie, ZBUF or SBUF) showed no risk of renal injury with these therapies.[29] The results reported herein corroborate this finding, as we observed a null effect of continuous ultrafiltration on AKI or renal failure, although the GRADE quality of evidence is very low. Taken all together, prospective randomized studies show no evidence that any type of ultrafiltration causes AKI. Collaboration among cardiac surgeon, anesthetist, and clinical perfusionists is critical to optimize the oxygen delivery during CPB, along with the patient's hemodynamics, and should avoid any low-flow or hypovolemic states in the perioperative period to prevent pre-renal or renal forms of AKI.

Assessment of bleeding outcomes was infrequently reported in the included studies. A minor, clinically insignificant, reduction in chest tube output was observed, and no difference in RBC transfusion. A reduction in bleeding complications, particularly with noncontinuous MUF or CUF used at the end of CPB, arises from hemoconcentration of blood cells and coagulation factors.[4,6] Continuous forms of ultrafiltration usually feature a near-neutral volume balance (ZBUF or SBUF) and conceptually do not achieve the same effect. Of all included studies, only Foroughi et al.[22] used MUF following continuous ultrafiltration during CPB and reported a substantial reduction in the measure of total chest tube output of 190.00 mL (95% CI: 4.17-375.85) but did not report transfusions. Important to note is that no evidence indicates increased bleeding with continuous forms of ultrafiltration.

The proposed immunomodulatory effects of continuous ultrafiltration often illicit concerns of postoperative infection. In fact, pneumonia was substantially reduced with continuous ultrafiltration but had low GRADE quality of evidence. This result was driven largely by results of the study by Matata et al.,[23] which involved moderate- or high-risk patients. Reporting of sternal wound infection or mediastinitis was minimal (2 studies) and did not show any increased risk with continuous ultrafiltration, but the estimate is largely imprecise, and overall, it has a very low quality of evidence. Overall, no evidence shows that continuous ultrafiltration increases the risk of postoperative infection.

Although this systematic review followed a prespecified protocol and included RCTs, its relative limitations should be considered when interpreting the results. The first is that the meta-analyses include trial-level, but not patient-level, data derived from included studies that generally were grossly underpowered and lacked the methodological rigor of high-quality RCTs, such as prespecified trial design, power calculation, randomization sequence, and blinded assessment of outcomes. The second limitation is heterogeneity of surgical era, patient populations, surgical procedures, continuous ultrafiltration protocols, and institutional postoperative management plans among included trials. A third limitation is the inconsistent reporting of important postoperative outcomes. Ventilation time and ICU LOS were the most commonly reported, in 9 and 8 of 12 studies, respectively, whereas all other outcomes appeared in 6 or fewer. This indicates a significant chance of selective reporting and decreases the quality of the outcome-specific analyses. Further in this regard, ultrafiltration protocols under study were poorly described and lacked standardized metrics to aid in interpretation of the therapy. The final limitation arises from the low certainty of evidence that occurs with imprecise estimates; our results should be interpreted cautiously, as our primary outcome was found to be statistically neutral, whereas key secondary outcomes favoured continuous ultrafiltration.

Conclusion

Continuous ultrafiltration during adult cardiac surgery has been studied in 12 single-centre RCTs, and the meta-analysis produced results with very low to low GRADE quality of evidence. A suggestion of operative mortality reduction with continuous ultrafiltration failed to meet statistical significance. Significant reductions in ICU LOS, ventilation time, and postoperative incidence of pneumonia were seen in continuous ultrafiltration groups, compared to controls. The therapy is safe, as no increased risk of AKI or renal failure or sternal wound infection was observed. These results present a state of equipoise for a well-powered RCT to further investigate whether the multiple physiological benefits of continuous ultrafiltration enhance recovery after adult cardiac surgery with CPB.

Ethics Statement

Ethics review board approval: not applicable.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.03.009.