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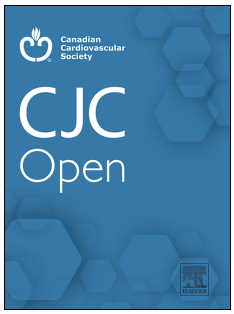

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Continuous Ultrafiltration Enhances Recovery after Adult Cardiac Surgery with Cardiopulmonary Bypass: A Systematic Review and Meta-Analysis

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Glossary of Abbreviations

AVR: aortic valve replacement

CABG: coronary artery bypass grafting

CI: confidence interval

CPB: cardiopulmonary bypass

CUF: conventional ultrafiltration

DUF: dilutional ultrafiltration

eGFR: estimated glomerular filtration rate

ICU: intensive care unit

LOS: length of stay

MD: mean difference

MUF: modified ultrafiltration

NR: not recorded

RCT: randomized controlled trial

RBC: red blood cell

SMUF: simple modified ultrafiltration

SBUF: subzero-balance ultrafiltration

UF: ultrafiltration

ZBUF: zero-balance ultrafiltration

Abstract

Background: Cardiac surgery with cardiopulmonary bypass is associated with systemic inflammation. Ultrafiltration used throughout the CPB 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 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 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 included. Compared to controls, patients receiving continuous ultrafiltration had no statistical difference in operative mortality, risk ratio of 0.32 (95% CI: 0.10 – 1.03; p=0.06). There was a reduction in ICU LOS of 7.01 (95% CI: 1.86 – 12.15; p=0.008) hours, ventilation time of 2.11 (95% CI: 0.71 – 3.51; p=0.003) hours, and pneumonia with risk ratio of 0.33 (95% CI: 0.15 – 0.75; p=0.008). There was no 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 pneumonia. A multi-center randomized trial could confirm and generalize these findings.

Introduction

Cardiac surgery and cardiopulmonary bypass (CPB) feature multiple pro-inflammatory 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, endothelial leak yielding cardiopulmonary and vasomotor dysfunction which is prohibitive to a timely post-operative 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 routinely utilized.

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 pro-inflammatory mediators.[4] Ultrafiltration protocols can vary widely in terms of duration of use, rate of effluent removal and volume balance targets. Non-continuous forms of ultrafiltration, such as conventional ultrafiltration (CUF) and modified ultrafiltration (MUF), are used for brief periods of time at the end of CPB or after the patient is weaned. A reduction in bleeding complications, by hemoconcentration of blood cells and coagulation factors, have 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 (DUF) – are used throughout the entire CPB time.

Continuous ultrafiltration presents an opportunity to actively extract circulating pro-inflammatory 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 post-operative period. The objective of this systematic review and meta-analysis of randomized trials, is to investigate if continuous forms of ultrafiltration yield immediate post-operative clinical benefits that matches the proposed therapeutic mechanism for adults undergoing cardiac surgery.

Methods

The protocol for this systematic review and metanalysis was previously published and registered in PROSPERO 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 (LB) designed the systematic search strategy in MEDLINE (Ovid MEDLINE All), Embase (Elsevier), the Cochrane Central Registry of Controlled Trials (CENTRAL) and Scopus (Elsevier) and executed it on November 3, 2021, dated back to database inception. Key search terms included: "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 in Supplemental Tables S2-S5 and summary of systematic search is in Supplemental Table S6.

Study Selection Criteria and Risk of Bias

Studies were selected for inclusion if they met the prespecified criteria: 1) randomized controlled trial study design, 2) participants with age greater than 18 years undergoing cardiac surgery and CPB, 3) intervention was any type of continuous ultrafiltration used throughout the entire CPB time (CUF, ZBUF, SMUF, DUF and combination techniques such as ZBUF-MUF), 4) comparator was a non-continuous form of ultrafiltration (CUF only used during rewarming or

MUF) or any non-interventional control and 5) studies were published in English. There was no exclusion based on patient sex, type of adult cardiac surgery, type of continuous ultrafiltration or ultrafiltration rate.

Two reviewers (JB and DH) independently screened the titles and abstracts identified by the systematic search using Covidence.[10] Furthermore, JB and DH independently screened the full texts to identify the RCTs that meet 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 JB and DH.[11] A third reviewer (RS) was available to arbitrate any disagreement in the study selection or risk of bias assessment processes.

Study Method, Demographics and Outcomes

JB and DH independently extracted pre-specified information about the included studies' methods, patient demographics and outcomes. Study methods included: the authors, publication date, randomization design, trial start and end date, 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 demographics included: sex, mean age, surgical risk (low-risk defined by STS or EuroScore II mortality risk score < 4, moderate- or high-risk defined by STS or EuroScore II mortality risk score > 4 or the presence of severe medical comorbidity or organ dysfunction), type of cardiac surgery (coronary bypass 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). Pre-specified

secondary outcomes were: invasive ventilation time, intensive care unit length of stay (ICU LOS), incidence or acute kidney injury (AKI) or renal failure, stroke, bleeding complications, sternal wound infection, pneumonia and patient-reported outcomes on post-operative recovery. There was no imputation of missing data.

Statistical Analysis

JB and DH independently extracted data from included studies, cross-referenced for accuracy, and imported into Review Manager V5.3 (RevMan) for analysis.[12] Dichotomous outcomes were analyzed by the inverse variance random-effects method, and expressed as risk ratios with 95% confidence intervals. Continuous outcomes were also analyzed by an inverse variance random-effects method, and expressed as mean difference with 95% confidence intervals. 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 only performed if there were at least two included studies reporting the same outcome. As stated in the pre-specified protocol, any statistically significant difference in the primary and key secondary outcomes were deemed clinically relevant.

Statistical heterogeneity was measured by the $\chi 2$ test ($p < 0.1$ indicating significant heterogeneity) and 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 ten or more studies report on an outcome. One pre-specified subgroup analysis was completed which differentiated patients by operative risk profile: 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 be 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 JB and DH, through the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[13] Domains that determine the certainty of result through GRADE include risk of bias, the 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 randomized controlled trials, consisting of 989 patients, included in the meta-analysis (Table 1).[14–25] There was a large range of study publication dates (1997-2020), types of continuous ultrafiltration used in the intervention arm (CUF, ZBUF, SBUF, CUF-MUF) and types of cardiac intervention (CABG, valvular, concomitant CABG-valve and aortic surgery). The intra-operative data from included studies is reported in Table 2. Mean CPB time ranged between 64 – 182 minutes and mean cross clamp time 32 – 145 minutes. Most studies reported the continuous ultrafiltration target, which featured widely varying protocols, while only half reported the total ultrafiltrate effluent volume, which again differed between trials (Table 2).

The majority of studies consisted of patients judged to have low operative risk while only 3 recent trials – Matata *et al.* (2015), Plotnikov *et al.* (2019) and Garcia-Camacho *et al.* (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 while older studies did not (Table 1). All studies were single-center design and lacked important methods such as sample size calculations and pre-specified study design and analysis. There was inconsistent reporting of post-operative outcomes of interest and a summary can be seen in Supplemental Table S7. One study was judged to be low risk of bias, four were judged to have moderate concerns on risk of bias while seven studies were judged to be at high risk of bias. Individual assessments of biases can be visualized in Table 3. The construction of Funnel plots was deferred as no outcome was reported by 10 or more studies.

Figure 1.

Operative Mortality

Four of the twelve included studies directly reported operative mortality on 502 patients (Figure 2). Overall, this outcome was rare and observed in 1.2% of the patients receiving ultrafiltration and 4.5% of the patients in the control groups; number needed to treat (NNT) = 30. The pooled analysis revealed a reduced risk of mortality with ultrafiltration by risk ratio (95% CI) of 0.32 (0.10 – 1.03) that did not reach statistical significance (p=0.06). There was consistency of effect between both risk subgroups and these results were heavily influenced by Matata *et al.* 2015 which contributed 86.4% of the analysis weight. The pooled analysis showed very low levels of heterogeneity ($I^2 = 0\%$). A pre-specified sensitivity analysis (Supplemental Figure S1) was conducted by removing Santarpino *et al.* 2009 and Zhang *et al.* 2009, at high risk of bias, which yielded a similar effect size with a more imprecise risk ratio (95% CI) of 0.32 (0.09 – 1.11) which only considers results from Matata *et al*. 2015.

Figure 2.

Intensive Care Unit Length of Stay

Eight of the twelve included studies directly report ICU LOS (hours) on 595 patients (Figure 3). There was a significant mean reduction (95% CI) in ICU LOS of 7.01 (1.86 – 12.15) hours (p=0.008) for patients receiving ultrafiltration compared to controls. This 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 ICU LOS but the

moderate- or high-risk subgroup showed a significantly larger effect size (p=0.02). There was a moderate degree of heterogeneity observed in the low-risk subgroup (I^2 = 73%), a low degree in the moderate- or high-risk subgroup (I^2 = 12%) and a high degree in the combined analysis (I^2 = 79%). A pre-specified sensitivity analysis (Supplemental Figure S2) was conducted by removing de Baar *et al.* 2003, Zhang *et al.* 2009, Zhang *et al.* 2011, Plotnikov *et al.* 2019 and Garcia-Camacho *et al.* 2020 as studies with high risk of bias. The resulting sensitivity analysis only included low-risk subgroup studies and the benefit of ultrafiltration on ICU LOS was neutralized with a reduction of 3.99 (-3.88 – 11.85) hours.

Figure 3.

Invasive Ventilation Time

Nine of the twelve included studies directly report ventilation time (hours) on 794 patients (Figure 4). Matata *et al.* 2015 reported this outcome in median and interquartile range which was converted to median and standard deviation for analysis with methods previously described.[26,27] There was a mean reduction (95% CI) of 2.11 (0.71 – 3.51) hours (p=0.003) for patients receiving ultrafiltration compared to controls. This represents a 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. There was a very high degree of heterogeneity observed in the low-risk subgroup (I^2 = 90%), moderate- or high-risk subgroup (I^2 = 96%) and the combined analysis (I^2 = 92%). A pre-specified sensitivity analysis (Supplemental Figure S3) was conducted by removing de Baar *et al.* 2003, Zhang *et al.* 2009, Zhang *et al.* 2011, Plotnikov *et al.* 2019 and Garcia-Camacho *et al.* 2020 as studies with

high risk of bias. The benefit of ultrafiltration was neutralized with an insignificant increase in ventilation time of 0.30 (-2.09 – 2.70) hours.

Figure 4.

Acute Kidney Injury or Renal Failure

Seven of the twelve included studies directly reported AKI or renal failure requiring dialysis on 654 patients (Figure 5). Babka *et al.* 1997, Santarpino *et al.* 2009, Zhang *et al.* 2009 and Foroughi *et al.* 2014 reported AKI without dialysis; all in the low-risk subgroup. Matata *et al.* 2015 and Plotnikov *et al.* 2019 reported renal failure requiring dialysis while Garcia-Camacho *et al.* 2020 reported renal failure without specifying the need for dialysis. There was no difference between ultrafiltration and control groups with a risk ratio (95% CI) of 0.84 (0.48 – 1.48). Renal injury was infrequent in the low-risk subgroup at 4.1% while more considerable in the moderate- or high-risk subgroup at 40%, largely driven by Matata *et al.* 2015 which enrolled patient with considerable pre-operative renal insufficiency indicated by eGFR 15-60 ml/min.

The comparison within the low-risk subgroup had a largely imprecise risk ratio (95% CI) of 1.56 (0.43 – 5.68), the moderate- or high-risk subgroup showed decreased risk of renal failure with ultrafiltration 0.70 (0.36 – 1.34) that did not reach statistical significance. There was a low degree of heterogeneity observed in the low-risk subgroup (I^2 = 11%), the moderate- or high-risk subgroup (I^2 = 25%) and the combined analysis (I^2 = 25%). A pre-specified sensitivity analysis (Supplemental Figure S4) was conducted by removing Babka *et al.* 1997, Santarpino *et al.* 2009, Zhang *et al.* 2009, Plotnikov *et al.* 2019 and Garcia-Camacho *et al.* 2020 as studies with high risk of bias. This analysis confirmed there was no difference between ultrafiltration and control with a risk ratio (95% CI) of 0.95 (0.58 – 1.55).

Figure 5.

Pneumonia

Four of the twelve included studies directly reported pneumonia on 437 patients (Figure 6). This outcome was rare and observe in 2.8% of the patient's receiving ultrafiltration and 9.6% of the patients in the control groups; NNT=15. There was a substantial reduction with ultrafiltration yielding a risk ratio (95% CI) of 0.33 (0.15 – 0.75) (p=0.008). This finding was consistent in both the low-risk and moderate- or high-risk subgroups. There was a very low degree of heterogeneity observed in the low-risk subgroup (I^2 = 0%) and combined analysis (I^2 = 0%). There was no indication for a sensitivity analysis.

Figure 6.

Chest Tube Bleeding

Five of the twelve included studies directly reported chest tube output (ml) on 520 patients (Figure 7). There was a mean reduction (95% CI) with ultrafiltration of 44.03 (4.21 – 83.85) ml compared to control (p=0.03). This represents a minor 8% reduction in Total Chest Tube Output from the 525.92ml weighted average observed in control patients. There was a larger degree of bleeding reduction with ultrafiltration in the low-risk subgroup compared to the moderate- or high-risk subgroup (p=0.04). There was a low degree of heterogeneity observed in the low-risk subgroup (I^2 = 0%) and moderate- or high-risk subgroup (I^2 = 3%) while the combined analysis showed a moderate level of heterogeneity (I^2 = 31%). A pre-specified sensitivity analysis (Supplemental Figure S5) was conducted by removing Zhang *et al.* 2011 and

Plotnikov *et al.* 2019 with high risk of bias. The combined sensitivity analysis yielded a mean reduction (95% CI) in the ultrafiltration group of 71.53 (-41.34 – 184.40) ml that did not reach statistical significance. The low-risk subgroup maintained a significant bleeding reduction of 150.60 (14.91 – 286.30) ml in the ultrafiltration group compared to controls while Matata *et al.* 2015 in the moderate- or high-risk subgroup yielded a non-statistical significant mean reduction of 10.00 (-33.18 – 53.18) ml with ultrafiltration.

Figure 7.

RBC Transfusion

Only four of the twelve included studies directly reported RBC transfusion (units/patient) on 304 patients (Figure 8). There was a mean reduction (95% CI) with ultrafiltration of 0.81 (-0.36 – 1.98) units/patient compared to controls that did not reach statistical significance (p=0.17). There was no subgroup analysis as all included studies were in the low-risk group. There was an exceedingly high degree of heterogeneity observed (I^2 = 93%). A sensitivity analysis was not completed as all four studies were judged to be at high risk of bias.

Figure 8.

Sternal Wound Infection or Mediastinitis

Only two of the twelve included studies directly reported sternal wound infection or mediastinitis on 319 patients (Figure 9). This outcome was rare and observed in 0.6% of the patient's receiving ultrafiltration and 2.4% of the patients in the control groups. Zhang *et al.* 2009 reported sternal wound complications while Matata *et al.* 2015 reported mediastinitis.

There was no difference between ultrafiltration and control groups with a risk ratio (95% CI) of 0.34 (0.05 – 2.18). There was no subgroup analysis as all included studies were in the low-risk group. There was a very low degree of heterogeneity observed ($I^2 = 0\%$). There was no indication for sensitivity analysis.

Figure 9.

Stroke

Stroke was infrequently reported and exceedingly rare. There was only one event in 220 patients over 3 studies. This occurred in the control arm of Zhang *et al* 2009.

Quality of Evidence

The quality of evidence for the reported outcomes cam 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 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 he analyzed studies were at high risk of bias. Imprecision commonly downgraded the quality ratings for dichotomous outcomes as confidence intervals 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 between studies was a serious issue for ventilation time, AKI or renal failure, RBC transfusion. Publication bias was generally suspected given the selective reporting

of outcomes observed between 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 favoring ultrafiltration.

Discussion

This systematic review and meta-analysis of randomized controlled trials 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 number needed to treat of 30. The result was heavily weighted from Matata *et al.* 2015 which enrolled moderate and high-risk patients with pre-operative renal insufficiency. Although this is 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 the systemic inflammation and enhancing cardiopulmonary function could explain this consistent finding. The effect size was four times larger in the moderate- or high-risk subgroup (20.24 hour reduction) than the low-risk subgroup (5.04 hour reduction) which suggest vulnerable patients at high operative risk might receive more benefit from continuous ultrafiltration. There was a substantial amount of heterogeneity in this outcome which 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 clinically-significant 18% reduction in ventilation time compared to controls. Unfortunately, there was an extreme burden of heterogeneity through all parts of this outcome analysis with similar rationale as the heterogeneity found in ICU LOS. Furthermore, data from Matata *et al.* 2015 was 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 post-operative 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 pro-inflammatory mediators during 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 post-operative period. Second, by targeting a slight negative volume balance through the ultrafiltration protocol, volume overload is avoided. This 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 which maintain normal acid-base parameters in the intra- and post-operative 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 non-continuous ultrafiltration (ie. MUF) as well as continuous forms (ie. ZBUF or SBUF) showed no risk of renal injury with these therapies.[29] The results here reported corroborate this as we observed a null effect of continuous ultrafiltration on AKI or renal failure, although the GRADE quality of evidence is very low. Taken altogether, there is no evidence from prospective randomized studies that any type of ultrafiltration causes acute kidney injury. Collaboration between cardiac surgeon, anesthetist and clinical perfusionists is critical to optimize the oxygen delivery during CPB, the patient's hemodynamics and should avoid any low flow or hypovolemic states in the peri-operative period to prevent pre-renal or renal forms of AKI.

Assessment of bleeding outcomes was infrequently reported in the included studies. There was a minor, clinically insignificant, reduction in chest tube output and no difference in RBC transfusion. A reduction in bleeding complications, particularly with non-continuous 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.* 2014 used MUF following continuous ultrafiltration during CPB and reported a substantial reduction in Total Chest Tube Output of 190.00 (4.17 – 375.85) ml but did not report transfusions. Importantly, there is no evidence of increased bleeding with continuous forms of ultrafiltration.

The proposed immunomodulatory effects of continuous ultrafiltration often illicit concerns of post-operative infection. In fact, pneumonia was substantially reduced with continuous ultrafiltration but had low GRADE quality of evidence. This result was largely driven by Matata *et al* 2015 consisting of moderate- or high-risk patients. There was scarce

reporting sternal wound infection or mediastinitis (two studies) which did not show any increased risk with continuous ultrafiltration, but the estimate is largely imprecise and overall has a very low quality of evidence. Overall, there is no evidence that continuous ultrafiltration increases risk of post-operative infection.

Although this systematic review followed a pre-specified protocol and included randomized controlled trials, there are relative limitations that 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 randomized controlled trials such as pre-specified 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 post-operative management plans between included trials. A third limitation is the inconsistent reporting of important post-operative outcomes. Ventilation time and ICU LOS were the most commonly reported, nine and eight of twelve studies respectively, while all other outcomes appeared in six or less. This indicates the significant change of selective reporting and decreases the quality of the outcome-specific analyses. Further to this, ultrafiltration protocols under study were poorly described and lacked standardized metrics to aid in interpretation of the therapy. The final limitation arises from low certainty of evidence with imprecise estimates; our results should be interpreted cautiously as our primary outcome was found to be statistically neutral while key secondary outcomes favored continuous ultrafiltration.

Conclusion

Continuous ultrafiltration during adult cardiac surgery has been studied in twelve single-center randomized controlled trials and the meta-analysis produced results with very low to low GRADE quality of evidence. There was a suggestion of operative mortality reduction with continuous ultrafiltration that failed to meet statistical significance. There were significant reductions in ICU LOS, ventilation time, and post-operative pneumonia in continuous ultrafiltraiton groups compared to controls. The therapy is safe as there was no increased risk of AKI or renal failure or sternal wound infection. These results present equipoise for a well-powered randomized controlled trial to further investigate if the multiple physiologic benefits of continuous ultrafiltration enhance recovery after adult cardiac surgery with CPB.

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Table 1. Patient Characteristics of Included Studies

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

CABG: coronary artery bypass grafting; CUF: conventional ultrafiltration; eGFR: estimated glomerular filtration rate; kg: kilogram; LVEF: left ventricular ejection fraction; min: minute; ml: milliliter; MUF: modified ultrafiltration; NR: not recorded; SBUF: subzero-balance ultrafiltration; UF: ultrafiltration; ZBUF: zero-balance ultrafiltration.

[a]Steroids were methylprednisolone 15 ml/kg at anesthesia induction.

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Table 2. Operative Characteristics of Included Studies

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

CABG: coronary artery bypass grafting; CUF: conventional ultrafiltration; eGFR: estimated glomerular filtration rate; kg: kilogram; LVEF: left ventricular ejection fraction; min: minute; ml: milliliter; MUF: modified ultrafiltration; NR: not recorded; SBUF: subzero-balance ultrafiltration; UF: ultrafiltration; ZBUF: zero-balance ultrafiltration.
[a]Steroids were methylprednisolone 15 ml/kg at anesthesia induction.

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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.* 1997	Concerns[a] 🟠	Low Risk 🟢	Low Risk 🟢	High Risk[b] 🔴	Concerns[c] 🟠	High Risk 🔴
Tallman *et al.* 2002	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Concerns[c] 🟠	Concerns 🟠
de bar *et al.* 2003	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	High Risk[b] 🔴	Concerns[c] 🟠	High Risk 🔴
Kuntz *et al.* 2006	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Concerns[c] 🟠	Concerns 🟠
Luciani *et al.* 2009	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Concerns[c] 🟠	Concerns 🟠
Santarpino *et al.* 2009	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	High Risk[b] 🔴	Concerns[c] 🟠	High Risk 🔴
Zhang *et al.* 2009	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	High Risk[b] 🔴	Concerns[c] 🟠	High Risk 🔴
Zhang *et al.* 2011	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	High Risk[b] 🔴	Concerns[c] 🟠	High Risk 🔴
Foroughi *et al.* 2014	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢
Matata *et al.* 2015	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	Concerns[c] 🟠	Concerns 🟠
Plotnikov *et al.* 2019	Low Risk 🟢	Low Risk 🟢	Low Risk 🟢	High Risk[b] 🔴	Concerns[c] 🟠	High Risk 🔴
Garcia-Camacho *et al.* 2020	Low Risk 🟢	High Risk[d] 🔴	High Risk[e] 🔴	Low Risk 🟢	Concerns[c] 🟠	High Risk 🔴

[a] Unbalanced groups after randomization
[b] No blinding
[c] No pre-specified analysis or reporting plan
[d] Multiple patients received different therapies than assigned due to clinical criteria
[e] Multiple patients excluded from analysis after randomization

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Table 4. GRADE Certainty of Evidence and Summary of Findings.

Participants (studies)	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 RCTs)	serious[e]	not serious	serious[a]	serious[b]	publication bias strongly suspected[c]	⨁◯◯◯ **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 RCTs)	serious[e]	not serious	serious[a]	not serious	none	⨁⨁◯◯ **Low**	-	-	-	-	MD **7.01 hours lower** (12.15 lower to 1.86 lower)
Invasive Ventilation Time											
794 (9 RCTs)	not serious	serious[d]	serious[a]	not serious	none	⨁⨁◯◯ **Low**	-	-	-	-	MD **2.11 hours lower** (3.51 lower to 0.71 lower)
Acute Kidney Injury or Renal Failure											
654 (7 RCTs)	serious[e]	serious[d]	very serious[a]	serious[b]	publication bias strongly suspected[c]	⨁◯◯◯ **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)
Total Chest Tube Output											
520 (5 RCTs)	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[c]	⨁⨁◯◯ **Low**	-	-	-	-	MD **44.03 ml lower** (83.85 lower to 4.21 lower)
Red Blood Cell Transfusion											
244 (3 RCTs)	serious[e]	serious[d]	not serious	serious[b]	publication bias strongly suspected[c]	⨁◯◯◯ **Very low**	-	-	-	-	MD **1.06 units/patient lower** (2.83 lower to 0.7 higher)
Sternal Wound Infection											
319 (2 RCTs)	serious[e]	not serious	not serious	very serious[f]	publication bias strongly suspected[c]	⨁◯◯◯ **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)
Pneumonia											
437 (4 RCTs)	serious[e]	not serious	serious[a]	not serious	publication bias strongly suspected[c]	⨁⨁◯◯ **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)

CI, confidence interval; MD, mean difference; RCT: randomized controlled trial; RR: risk ratio.
[a.] Differences in surgical population and procedures
[b.] 95% CI includes null
[c.] Selective reporting of outcomes between included studies
[d.] Opposite polarity of effect between studies
[e.] More than half of analyzed studies show high risk of bias
[f.] 95% CI is considerably wide
[g.] Opposite polarity of effects between low and high-risk groups

Figure Legend

Figure 1. Consort Flow Diagram.

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.

Figure 3. Intensive Care Unit Length of Stay Forest Plot. Mean difference comparison of ICU LOS in hours between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

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.

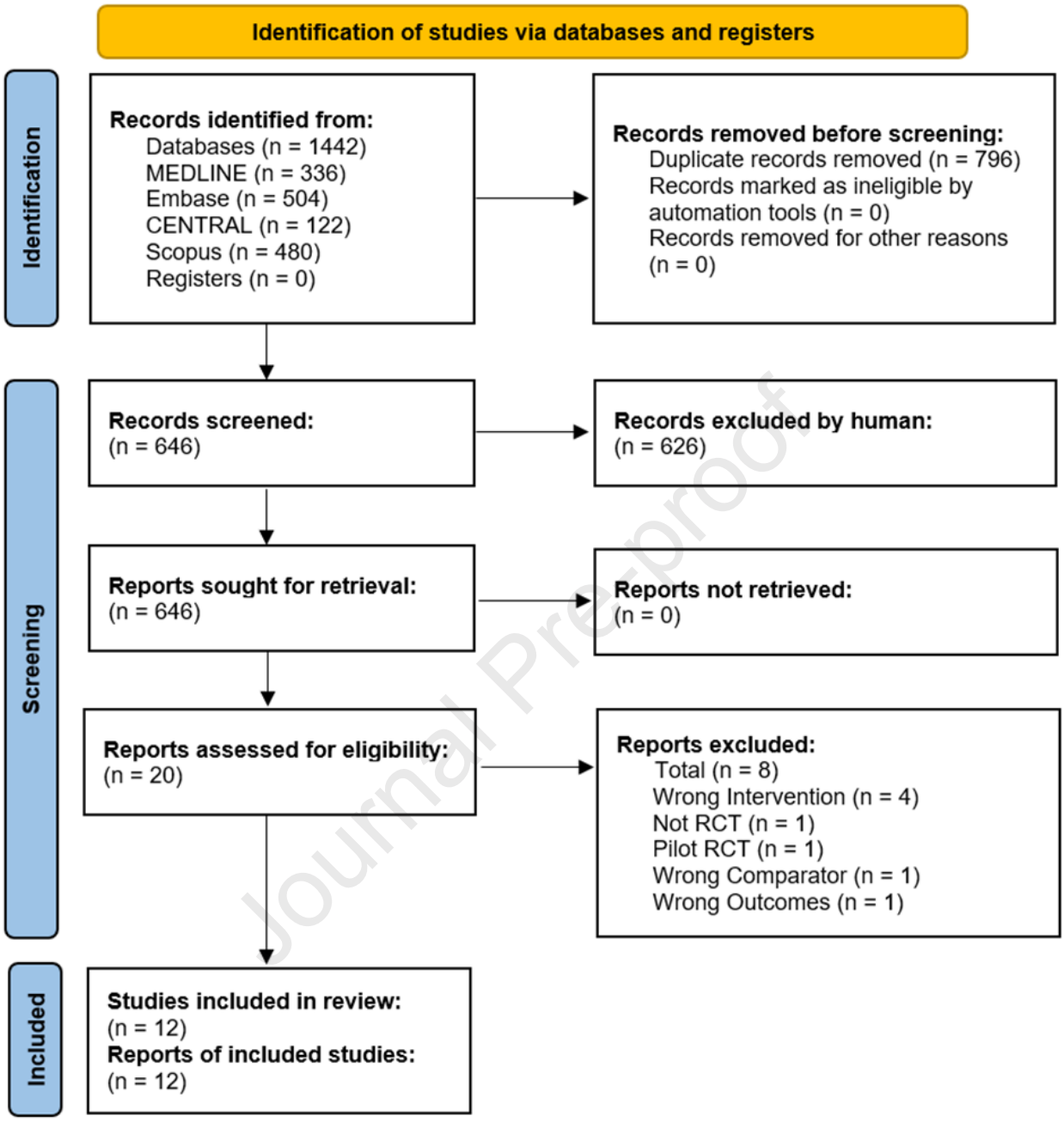
Figure 5. Acute Kidney Injury or Renal Failure Forest Plot. Comparison of AKI or renal failure events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

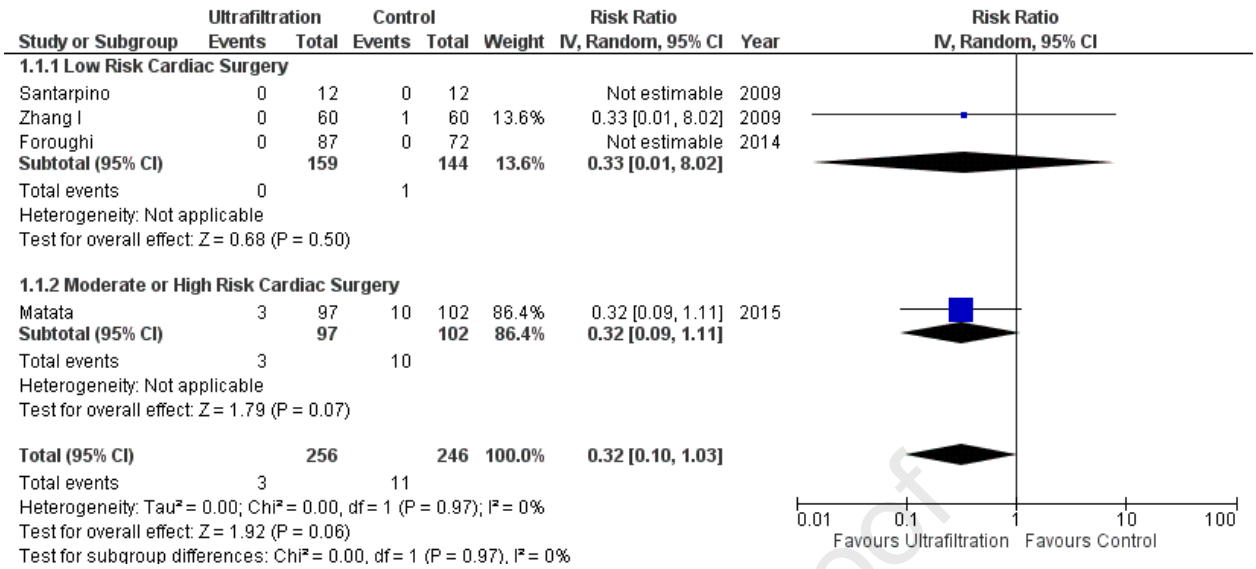
Figure 6. Pneumonia Forest Plot. Comparison of post-operative pneumonia events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.

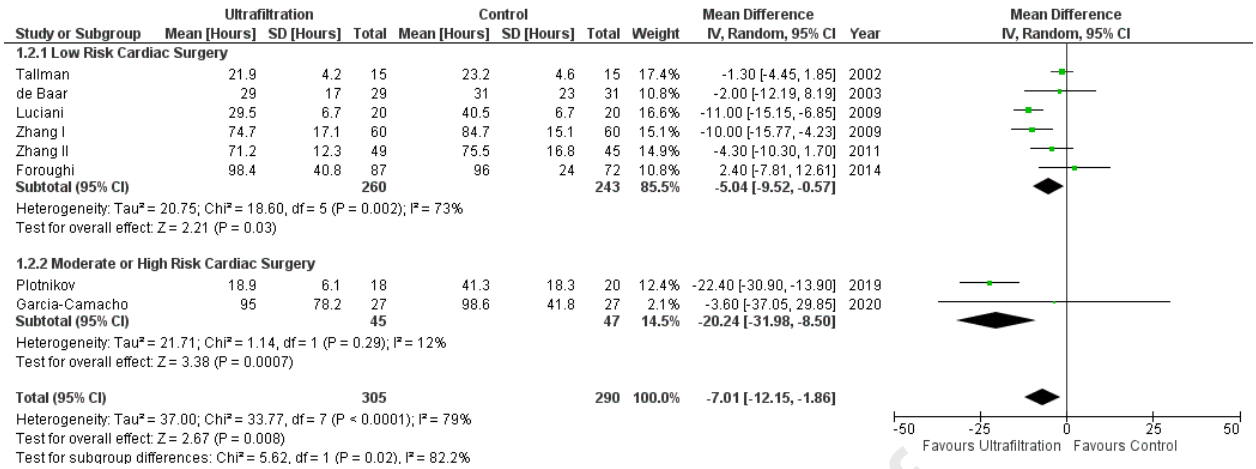
Figure 7. Total Chest Tube Output Forest Plot. Mean difference comparison of chest tube output in milliliters between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom; ml, milliliter.

Figure 8. 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.

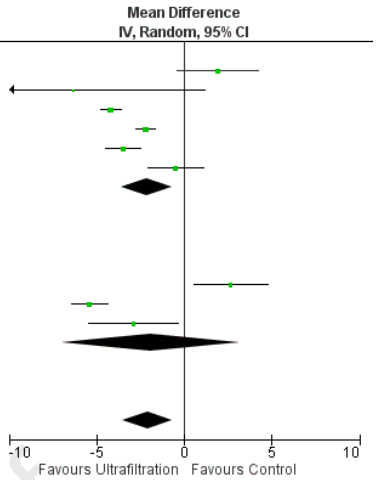
Figure 9. Sternal Wound Infection Forest Plot. Comparison of post-operative sternal wound infection events between continuous forms of ultrafiltration and control groups. CI, confidence interval; df, degrees of freedom.



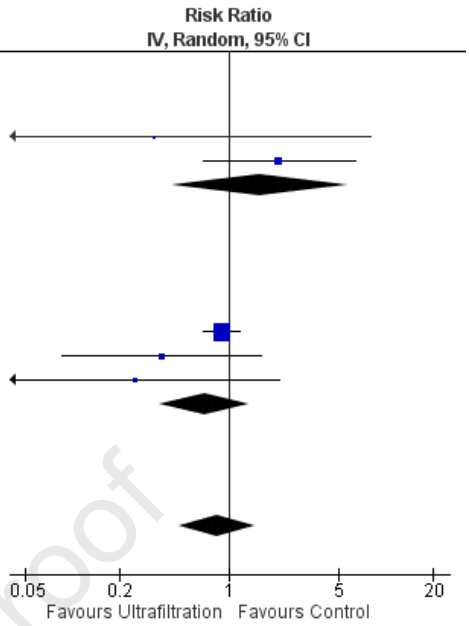


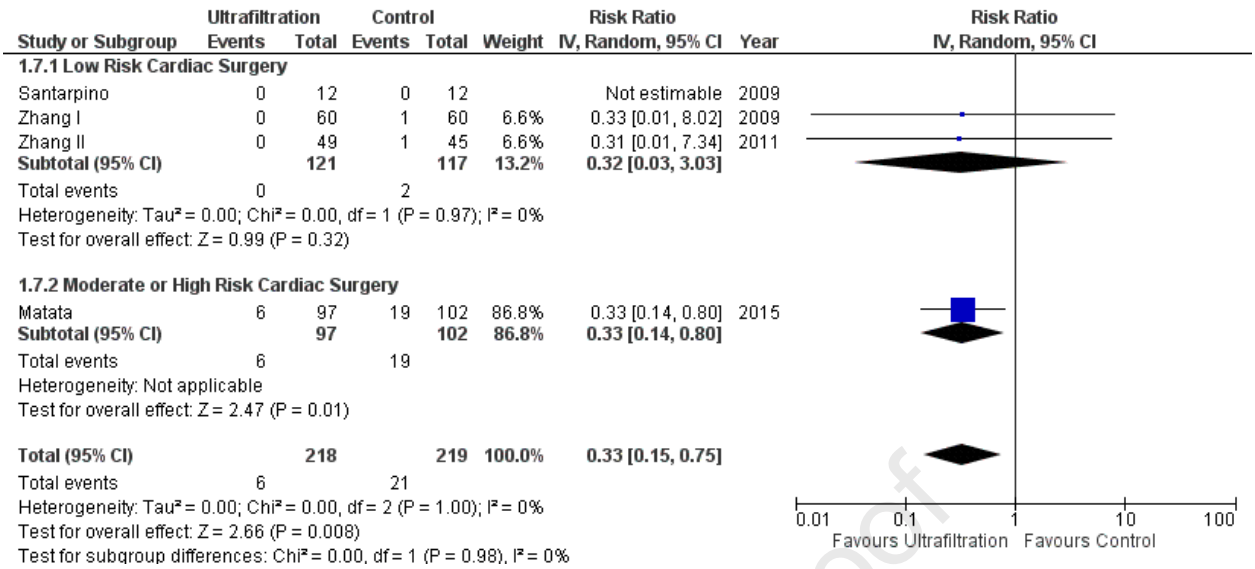


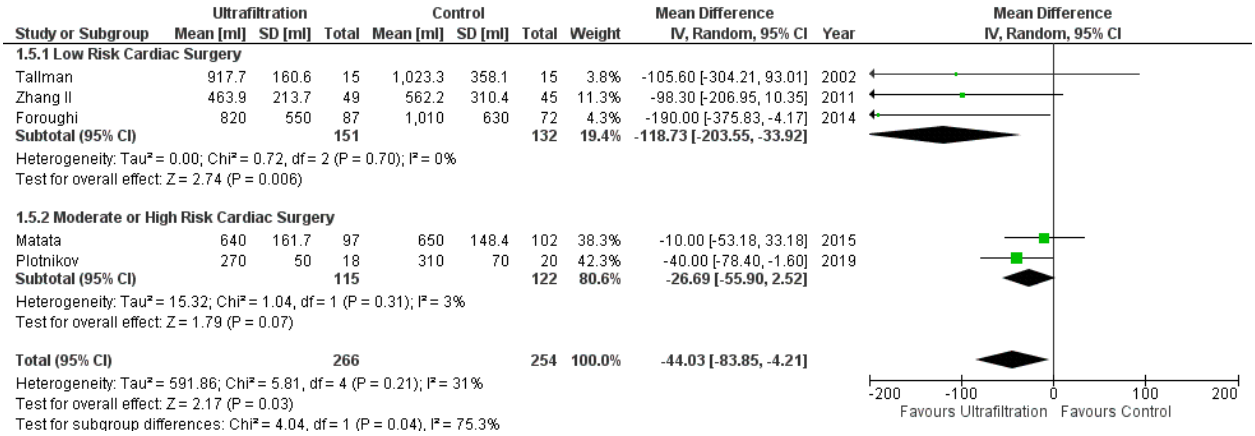
Study or Subgroup	Ultrafiltration Mean [Hours]	SD [Hours]	Total	Control Mean [Hours]	SD [Hours]	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.3.1 Low Risk Cardiac Surgery									
Tallman	10.2	3.9	15	8.3	2.3	15	10.3%	1.90 [-0.39, 4.19]	2002
de Baar	17	3.6	29	23.3	21	31	2.8%	-6.30 [-13.81, 1.21]	2003
Zhang I	14.4	1.7	60	18.6	1.6	60	13.9%	-4.20 [-4.79, -3.61]	2009
Luciani	3.6	0.9	20	5.8	0.9	20	13.9%	-2.20 [-2.76, -1.64]	2009
Zhang II	14.5	2.43	49	18	2.4	45	13.3%	-3.50 [-4.48, -2.52]	2011
Foroughi	10	4.7	87	10.5	5.4	72	12.0%	-0.50 [-2.09, 1.09]	2014
Subtotal (95% CI)			**260**			**243**	**66.3%**	**-2.14 [-3.59, -0.69]**	
Heterogeneity: Tau² = 2.39; Chi² = 52.45, df = 5 (P < 0.00001); I² = 90%									
Test for overall effect: Z = 2.90 (P = 0.004)									
1.3.2 Moderate or High Risk Cardiac Surgery									
Matata	12	8.28	97	9.35	6.77	102	10.8%	2.65 [0.54, 4.76]	2015
Plotnikov	3.4	1.2	18	8.8	2	20	13.2%	-5.40 [-6.44, -4.36]	2019
Garcia-Camacho	5	2.3	27	7.9	6.4	27	9.6%	-2.90 [-5.47, -0.33]	2020
Subtotal (95% CI)			**142**			**149**	**33.7%**	**-1.93 [-7.02, 3.17]**	
Heterogeneity: Tau² = 19.26; Chi² = 45.57, df = 2 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 0.74 (P = 0.46)									
Total (95% CI)			**402**			**392**	**100.0%**	**-2.11 [-3.51, -0.71]**	
Heterogeneity: Tau² = 3.58; Chi² = 100.65, df = 8 (P < 0.00001); I² = 92%									
Test for overall effect: Z = 2.95 (P = 0.003)									
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%									



Study or Subgroup	Ultrafiltration Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
1.4.1 Low Risk Cardiac Surgery							
Babka	0	30	0	30		Not estimable	1997
Santarpino	0	12	0	12		Not estimable	2009
Zhang I	0	60	1	60	3.0%	0.33 [0.01, 8.02]	2009
Foroughi	10	87	4	72	18.5%	2.07 [0.68, 6.32]	2014
Subtotal (95% CI)		**189**		**174**	**21.4%**	**1.56 [0.43, 5.68]**	
Total events	10		5				
Heterogeneity: Tau² = 0.19; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%							
Test for overall effect: Z = 0.68 (P = 0.50)							
1.4.2 Moderate or High Risk Cardiac Surgery							
Matata	47	97	55	102	60.3%	0.90 [0.68, 1.18]	2015
Plotnikov	2	18	6	20	12.0%	0.37 [0.09, 1.61]	2019
Garcia-Camacho	1	27	4	27	6.3%	0.25 [0.03, 2.09]	2020
Subtotal (95% CI)		**142**		**149**	**78.6%**	**0.70 [0.36, 1.34]**	
Total events	50		65				
Heterogeneity: Tau² = 0.13; Chi² = 2.66, df = 2 (P = 0.26); I² = 25%							
Test for overall effect: Z = 1.08 (P = 0.28)							
Total (95% CI)		**331**		**323**	**100.0%**	**0.84 [0.48, 1.48]**	
Total events	60		70				
Heterogeneity: Tau² = 0.12; Chi² = 5.30, df = 4 (P = 0.26); I² = 25%							
Test for overall effect: Z = 0.59 (P = 0.55)							
Test for subgroup differences: Chi² = 1.20, df = 1 (P = 0.27), I² = 16.4%							







Study or Subgroup	Ultrafiltration Mean [Units]	Ultrafiltration SD [Units]	Ultrafiltration Total	Control Mean [Units]	Control SD [Units]	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Babka	0.6	1.3	30	0.75	1.5	30	25.2%	-0.15 [-0.86, 0.56]	1997
Santarpino	0.62	0.23	15	0.34	0.062	15	27.7%	0.28 [0.16, 0.40]	2009
Zhang I	1.54	1.56	60	3.64	2.677	60	24.7%	-2.10 [-2.88, -1.32]	2009
Zhang II	2.27	2.27	49	3.76	3.07	45	22.3%	-1.49 [-2.59, -0.39]	2011
Total (95% CI)			**154**			**150**	**100.0%**	**-0.81 [-1.98, 0.36]**	

Heterogeneity: Tau² = 1.28; Chi² = 44.76, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.36 (P = 0.17)