Interactive CardioVascular and Thoracic Surgery 32 (2021) 671–682
doi:10.1093/icvts/ivaa330 Advance Access publication 20 January 2021

STATE-OF-THE-ART

ADULT CARDIAC

Cite this article as: Low ZK, Gao F, Sin KYK, Yap KH. Modified ultrafiltration reduces postoperative blood loss and transfusions in adult cardiac surgery: a meta-analysis of randomized controlled trials. Interact CardioVasc Thorac Surg 2021;32:671–82.

Modified ultrafiltration reduces postoperative blood loss and transfusions in adult cardiac surgery: a meta-analysis of randomized controlled trials

Zhao Kai Low [a,*], Fei Gao [b,c], Kenny Yoong Kong Sin [d] and Kok Hooi Yap [a,d]

[a] Department of Cardiothoracic Surgery, KK Women's and Children's Hospital, Singapore, Singapore
[b] Department of Biostatistics, National Heart Centre Singapore, Singapore, Singapore
[c] Duke-NUS Medical School, Singapore, Singapore
[d] Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore, Singapore

* Corresponding author. Department of Cardiothoracic Surgery, KK Women's and Children's Hospital, Singapore, 100 Bukit Timah Road, Singapore 229899, Singapore. Tel: +65-82230321; e-mail: zhaokai.low@mohh.com.sg (Z.K. Low).

Received 7 August 2020; received in revised form 19 November 2020; accepted 28 November 2020

Key question

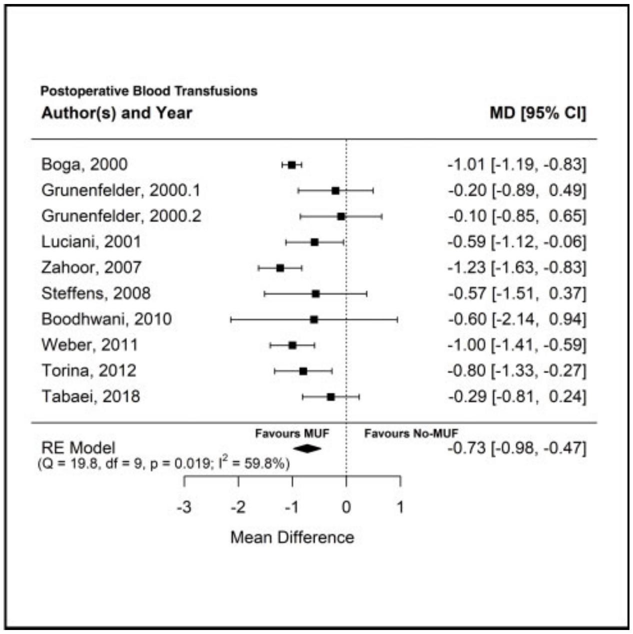
Does modified ultrafiltration (MUF) result in improved clinical outcomes after cardiopulmonary bypass in adult cardiac patients?

Key finding(s)

Improved post-bypass hematocrit levels; reduced chest tube bleeding, transfusion requirements and ICU stay after MUF.

Take-home message

MUF is safe and feasible for use in adult cardiac surgery patients, with improved clinical outcomes and no complications reported.



Abstract

OBJECTIVES: Cardiopulmonary bypass in cardiac surgery has been associated with several deleterious effects including haemodilution and systemic inflammation. Modified ultrafiltration (MUF) has been well established in paediatric cardiac surgery in counteracting post-perfusion syndrome. However, MUF is less commonly used in adult cardiac surgery. In this meta-analysis, we compared clinical outcomes in adult patients who underwent cardiopulmonary bypass with and without MUF.

METHODS: Electronic searches were performed using Pubmed, Ovid Medline, EMBASE and the Cochrane Library until April 2020. Selection criteria were randomized studies of adult cardiac surgery patients comparing MUF versus no MUF. Primary outcomes were post-operative mortality, haematocrit, blood transfusion, chest tube drainage, duration of intensive care unit (ICU) stay and duration of mechanical ventilation.

RESULTS: Thirteen randomized controlled trials were included, comprising 626 patients in the MUF group, and 610 patients in the control (no-MUF) group. There was a significantly improved postoperative haematocrit [mean difference 2.70, 95% confidence interval (CI) 0.68–4.73, $P = 0.009$], lower chest tube drainage (mean difference -105 ml, 95% CI -202 to -7 ml, $P = 0.032$), lower postoperative blood transfusion rate (mean difference -0.73 units, 95% CI -0.98 to -0.47 units, $P < 0.0001$) and shorter duration of ICU stay (mean difference -0.13 days, 95% CI -0.27 to -0.00 days, $P = 0.048$) in the MUF group. There was no difference in ventilation time (mean difference -0.47 h, 95% CI -2.05 to 1.12 h, $P = 0.56$) or mortality rates (odds ratio 0.62, 95% CI 0.28–1.33, $P = 0.22$). There were no reported complications associated with MUF.

CONCLUSIONS: MUF is a safe and feasible option in adult cardiac patients, with significant benefits including improved postoperative haematocrit, as well as reduced postoperative chest tube bleeding, transfusion requirements and duration of ICU stay.

Keywords: • Modified ultrafiltration • Conventional ultrafiltration • Cardiopulmonary bypass • Adult cardiac surgery • Clinical outcomes • Meta-analysis • Haematocrit • Blood transfusions •

ABBREVIATIONS

CI	Confidence interval
CPB	Cardiopulmonary bypass
CUF	Conventional ultrafiltration
ICU	Intensive care unit
MUF	Modified ultrafiltration
OR	Odds ratio
RCT	Randomized controlled trial
SIRS	Systemic inflammatory response syndrome

INTRODUCTION

The use of cardiopulmonary bypass (CPB) in cardiac surgery has been associated with several deleterious effects including haemodilution, coagulopathy and activation of a systemic inflammatory response [1–3]. The development of this inflammatory state is believed to be multifactorial, including operative trauma, ischaemia–reperfusion injury, endotoxaemia and contact of blood components with synthetic surfaces of the cardiopulmonary circuit [2, 3]. The clinical manifestations of this inflammatory response include haemodynamic alterations, increased vascular permeability and interstitial oedema, as well as cardiac, respiratory, renal, hepatic and even multiorgan dysfunction [3, 4].

The role of perioperative hemofiltration to counteract the effects of postperfusion syndrome has been well established [5–10]. The removal of excess fluid and lower molecular weight substances including inflammatory mediators under a hydrostatic pressure gradient results in haemoconcentration and attenuation of the postoperative systemic inflammatory response. Compared to conventional ultrafiltration (CUF) which is typically performed during the rewarming stage of CPB, modified ultrafiltration (MUF) is performed after termination of CPB and provides greater efficiency in filtration and haemoconcentration [11].

This has been well studied in the realm of paediatric cardiac surgery and anaesthesiology [10, 12–15], as the inflammatory response and haemodilutional effects of CPB are believed to be more pronounced in the paediatric population, especially in smaller children and infants [11, 16]. A previous meta-analysis of randomized controlled trials (RCTs) comparing MUF and CUF in paediatric cardiac patients demonstrated significantly higher post-bypass haematocrit and mean arterial blood pressures with MUF [17], which has been adopted as the standard of care in 75% of paediatric cardiac centres in North America [18]. In adult cardiac patients, a previous meta-analysis [5] of combined ultrafiltration techniques reported reduced postoperative bleeding, although there has been no meta-analysis solely focusing on the effects of MUF rather than CUF. This is likely to be of increasing relevance in contemporary and future adult cardiac surgical practice, where an increasing number of older patients with multiple comorbidities are undergoing cardiac surgery [19, 20]. These adult patients are at higher risk of postoperative complications such as perioperative myocardial infarction, acute respiratory distress syndrome and systemic inflammatory response syndrome (SIRS) [21, 22], and may stand to benefit from MUF after CPB. Furthermore, postoperative bleeding and blood transfusions continue to be a major contributor towards medical costs and resource utilization, and the potential beneficial effects of MUF on the coagulation system and reducing transfusion requirements is an important consideration in our current practice. Hence, we aimed to perform a systematic review and meta-analysis to examine the clinical outcomes of MUF in adult cardiac surgery with pooled data from RCT studies.

MATERIALS AND METHODS

Selection criteria

Randomized studies of patients undergoing adult cardiac surgery comparing MUF versus no-MUF during the surgery were included in this study. We only included full articles in English language. Our exclusion criterion was overlapping studies from the same institution and studies containing a single-arm treatment group. Where overlapping publications were found with the same cohort of patients, we used the data from the publication reporting the largest cohort and/or the most up-to-date data.

Literature search strategy

Electronic searches were performed using Pubmed, Ovid Medline, EMBASE and the Cochrane Library until September 2020. We combined medical subject headings (MeSH) terms and keywords for ultrafiltration, adult cardiac and thoracic surgery, and CPB. The reference lists of the full articles were also manually searched to identify eligible studies. The full electronic search strategy is appended in Supplementary Material, File 1.

Data extraction and critical appraisal of evidence

Two reviewers (K.H.Y. and Z.K.L.) independently assessed selected studies, and extracted and tabulated data from each article: first author, year of publication, study design, sample size, and outcome measures. The reviewers verified and reached consensus at each stage of the screening process, with a tabulated Cohen's kappa coefficient of 0.84 (92% agreement). Primary outcomes were postoperative mortality, haematocrit, blood transfusions, chest drainage volume, duration of intensive care unit (ICU) stay and duration of mechanical ventilation.

Assessments of methodological quality of included studies

All studies were randomized control studies for which the Jadad scale was used to assess their methodological quality. The Jadad scale is known for assessment of RCT-related literature [23]. It is composed of 5 points in total, 2 pertinent to randomization, 2 pertinent to blinding and one pertinent to dropout rate. When the study simply reports randomization and blinding without any detailed description, one point in each category is given. One additional point is given when there is detailed description of the appropriate method. Nevertheless, a point is deducted if the description is inappropriate. Moreover, when the number and reasons for dropouts are reported, one point is given. A total of ≥3 points are considered high quality. If it is impossible to perform a double-blinded study, it is regarded as high quality when the total score is ≥2 points. K.H.Y. and Z.K.L. independently assessed and assigned scores to each RCT included in this meta-analysis. The total scores from these 2 reviewers were then added up and the average scores were recorded.

Statistical analysis

Meta-analysis using a random-effects model was performed to determine the pooled effect estimates. The estimators of the treatment effects were expressed as the weighted mean difference with 95% confidence intervals (CIs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes (mortality). Mean was estimated using median and interquartile range when mean was not reported. The heterogeneity of collected data was assessed using a homogeneity test based on the χ^2 test. The I^2 statistic was used to assess the impact of heterogeneity on the results. Owing to the low power of this test, we conducted cumulative meta-analysis which allows detection of both temporal trends and publication bias. Sources of heterogeneity were examined using meta-regression with age, gender and Jadad scale as predictors. All statistical analyses were performed using R package metaphor [24].

RESULTS

Screening process and study selection

Our search strategy identified 6860 references pertaining to ultrafiltration and cardiac surgery. Screening of the titles and abstracts identified 23 references which were potentially eligible for review. These articles were reviewed in full and compared against our inclusion criteria, and 10 studies were excluded. Altogether 13 studies [25–37] were included in the quantitative meta-analysis, comprising 626 patients in the MUF group and 610 patients in the control group. Among these studies, 3 studies described the use of CUF in all patients undergoing CPB, followed by MUF in the treatment group, while the other studies did not utilize CUF. As an exception to the study selection criteria, Weber *et al.* [33] (published in 2011) and Papadopoulos *et al.* [35] (published in 2013) contained the study population, but both studies were retained for analysis as they reported different clinical outcomes relevant to this meta-analysis. The process of literature search and identification of eligible studies is summarized in Fig. 1.

Description of studies

The details and patient characteristics of the selected studies are summarized in Table 1. There were no significant differences in baseline patient characteristics including age and gender. All 13 studies were prospective, randomized controlled studies comparing the use of MUF versus no-MUF after CPB in adult cardiac surgery patients. The largest study was a single-centre RCT by Luciani *et al.* [29] with a total of 573 patients. Boodhwani *et al.* [32] and Tabaei *et al.* [37] performed double-blinded studies; the former involved the use of a 'sham' circuit without ultrafiltration, and the surgeon, anaesthesiologist and intensivist were blinded to the treatment allocation (although the surgeon could not be blinded successfully). Torina *et al.* [34] performed a partially

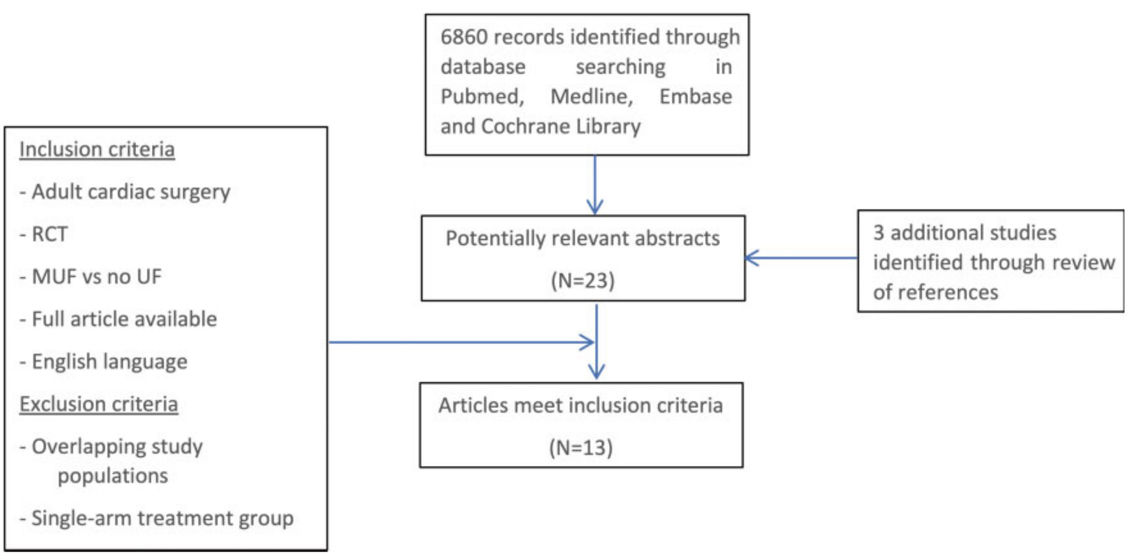


Figure 1: Meta-analysis flow chart. MUF: modified ultrafiltration; RCT: randomized controlled trial; UF: ultrafiltration.

Table 1: Summary of studies

Study	Year	Number of patients	Age	Male	Operations performed	Primary outcomes	Study quality[a]
Onoe *et al.* [25]	2000	CUF + MUF: 9	64.4 ± 9.3	NR	AVR 4, MVP 2, CABG 1, Bentall's 1, Dor's 1	Changes in haematocrit, systolic BP and IL-8 level	1
		CUF: 9	59.1 ± 18.2		AVR 6, CABG 2, MVR 1		
Grünenfelder *et al.* [26]	2000	Normothermic CPB: MUF 30, no-UF 20	62.1	NR	CABG	Intubation time, blood loss, transfusions, $PAaO_2$, inotropic requirement, complications (pulmonary infection, AF), ICU stay, hospital stay, WBC, CRP	1
		Hypothermic CPB: MUF 30, no-UF 17	58.7		CABG		
Boga *et al.* [27]	2000	MUF: 20	57.8 ± 8.9	80%	CABG	Postop haematocrit, transfusions, changes in CO, CI, SVR, PVR, IL-6, IL-8, neopterin	1
		No-UF: 20	61.2 ± 7.5	70%	CABG		
Leyh *et al.* [28]	2001	MUF: 16	59.6 ± 8.2	NR	CABG	Perioperative coagulation and fibrinolytic parameters, haematocrit, blood loss, transfusions	1
		No-UF: 16	64.3 ± 6.6		CABG		
Luciani *et al.* [29]	2001	MUF: 284	63.8 ± 10.6	65.8%	CABG 173, AVR 37, MVR 24, AVR/MVR 7, AVR/CABG 8, MVR/ CABG 5, others 35	Mortality, complications, inotropic requirement, intubation time, ICU stay, hospital stay, blood loss, transfusions	2
		No-UF: 289	62.6 ± 13.5	72.3%	CABG 173, AVR 37, MVR 24, AVR/MVR 7, AVR/CABG 8, MVR/CABG 5, others 35		
Zahoor *et al.* [30]	2007	MUF: 50	50.7 ± 14.7	70%	CABG 40, MVR 5, others 5	Postop hematocrit, haemoglobin, blood loss, transfusions, reoperation	3
		No-UF: 46	48.7 ± 11.2	86.9%	CABG 36, AVR 3, MVR 6, CABG/AVR 1		
Steffens *et al.* [31]	2008	MUF ± CUF: 10	58.4 ± 11.4	90%	CABG 6, AVR 2, MVR 2	Perioperative TEG and coagulation parameters, haemoglobin, blood loss, transfusions	1
		No-UF ± CUF: 9	57.6 ± 16.8	66.7%	CABG 5, AVR 3, AVR/ CABG 1		
Boodhwani *et al.* [32]	2010	MUF: 29	66.3 ± 13.1	34.5%	NR	Postop blood loss, transfusions, reoperation, inotropic requirement, mortality, hospital stay	4
		No-UF: 36	71.1 ± 10.1	22.2%	NR		
Weber *et al.* [33][b]	2011	MUF: 25	74 ± 6	52%	Complex cardiac surgery (combined procedures, double-valve surgery, aortic surgery, reoperations)	Perioperative MEA, TEG and coagulation parameters, haematocrit, blood loss, transfusions, reoperation	2
		No-UF: 25	75 ± 5	64%			
Torina *et al.* [34]	2012	MUF: 30	55.2 ± 7.3	80%	CABG	Postop blood loss, transfusions, ICU stay, hospital stay, inflammatory markers (IL-6, TNFR2, P-selectin, sICAM-1)	3
		No-UF: 30	55.6 ± 9.3	93.3%	CABG		
Papadopoulos *et al.* [35][b]	2013	MUF: 25	74 ± 6	52%	Complex cardiac surgery (combined procedures, double-valve surgery, aortic surgery, reoperations)	Postop blood loss, transfusions, reoperation, ICU stay, hospital stay, intubation time, inotropic requirements, complications, inflammatory markers (LBP, C5b9, IL-6, IL-10, IL-1beta, TNF-alpha)	2
		No-UF: 25	75 ± 5	64%			
Naveed *et al.* [36]	2016	MUF: 40	46.95 ± 13.24	72.5%	CABG 16, MVR 9, AVR 8, others 7	Postop bleeding, reoperation, ICU stay, mortality	2
		No-UF: 40	51.15 ± 8.9	82.5%	CABG 24, MVR 5, AVR 5, others 6		
Tabaei *et al.* [37]	2018	CUF + MUF: 28	60.3 ± 8.1	74%	CABG	Perioperative haemodynamic parameters, ICU stay, ventilation time, inflammatory markers (TNF-alpha, IL-6, IL-8, IL-10), haematocrit, blood transfusions, ROTEM parameters	3
		CUF: 28	58.43 ± 8.77	85%	CABG		

Values reported as mean ± standard deviation. All values for age and gender were reported as not significant, except Zahoor *et al.* (**P*-value = 0.04).

[a]Study quality reported according to Jadad scale: scored upon 5 (2 points for randomization, 2 points for blinding, 1 point for drop-out rate). A total of ≥3 points is considered high quality. If it is impossible to perform a double-blinded study, a total score of ≥2 points is considered as high quality.

[b]Weber *et al.* and Papadopoulos *et al.* contained the same study population. Both studies were retained for analysis as they contained different clinical outcomes relevant to the current meta-analysis.

AF: atrial fibrillation; AVR: aortic valve replacement; BP: blood pressure; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CRP: C-reactive protein; CUF: conventional ultrafiltration; ICU: intensive care unit; IL: interleukin; LBP: lipopolysaccharide-binding protein; MEA: multiple electrode aggregometry; MUF: modified ultrafiltration; MVP: mitral valvuloplasty; MVR: mitral valve replacement; No-UF: no ultrafiltration; NR: not reported; $PAaO_2$: pulmonary-alveolar O_2-gradient; sICAM-1: soluble intercellular adhesion molecule-1; TEG: thromboelastography; TNF-α: tumour necrosis factor-α; TNFR2: tumour necrosis factor receptor 2; WBC: white blood cell.

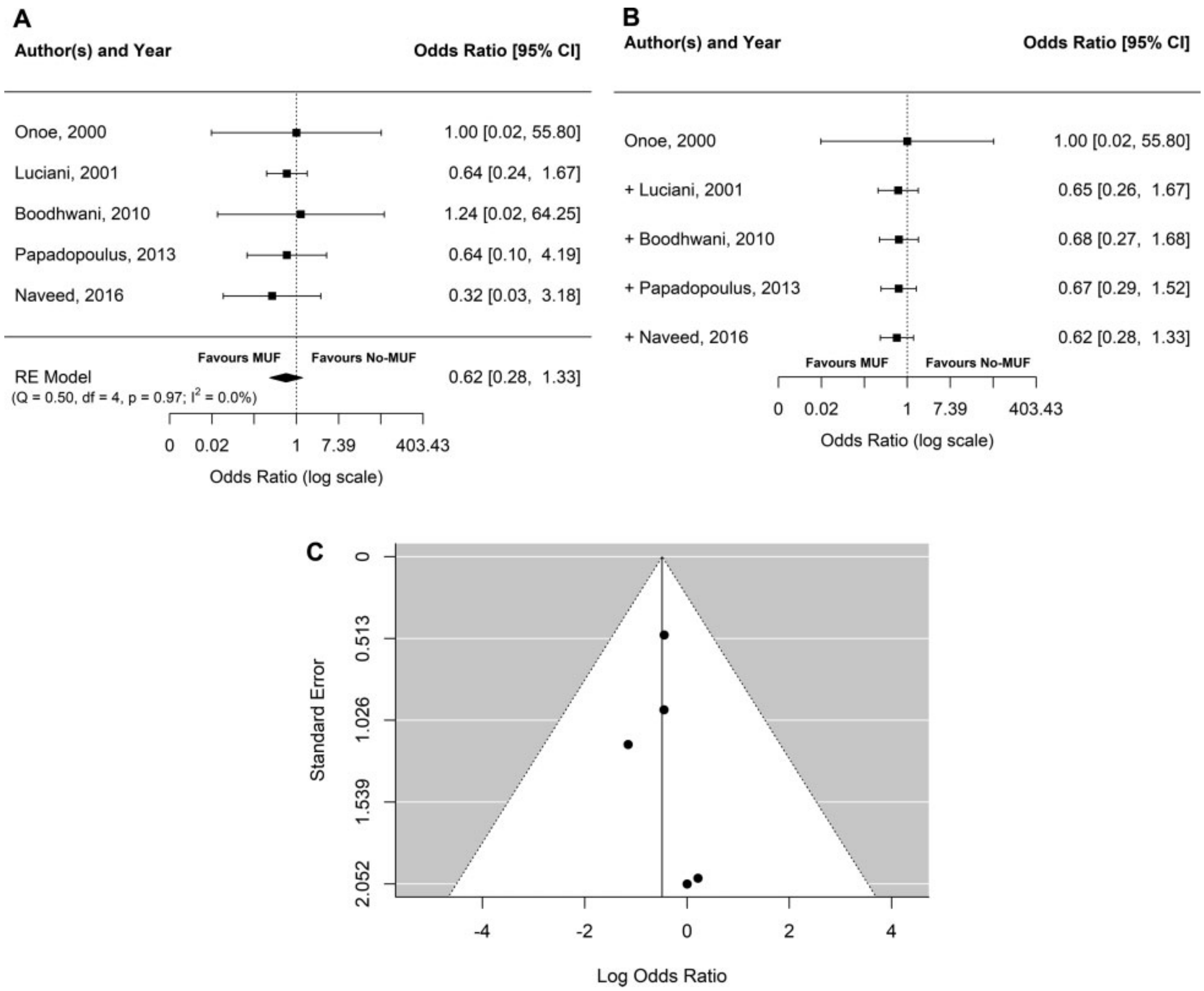


Figure 2: Meta-analysis outcomes for mortality in MUF compared with no-MUF. (**A**) Non-cumulative meta-analysis, (**B**) cumulative meta-analysis, (**C**) Funnel plot. CI: confidence interval; MUF: modified ultrafiltration; RE: random-effects.

blinded study where the intensivist was blinded, but not the surgeon or anaesthesiologist. The other studies were randomized but not blinded—these were regarded as high-quality studies if the Jadad score was ≥2 points, acknowledging the logistical challenges and low feasibility of blinding such studies. All studies utilized arteriovenous MUF in the treatment group, except Tabaei *et al.* [37] where the MUF configuration was not specified. Grünenfelder *et al.* [26] compared normothermic and hypothermic CPB, in which patients were further randomized into MUF and control groups. These were analysed separately in our statistical meta-analysis. Among the rest of the studies, 8 used hypothermic CPB, while the other 4 did not specify the temperature of CPB used.

None of the studies reported complications related to the use of MUF, such as technical complications, pulmonary air embolism, arrhythmias, hypothermia or sustained systemic hypotension.

Combined analysis

Meta-analysis results were presented as traditional forest plots as well as cumulative forest plots in order of publication year. This allows us to detect temporal trends and appreciate the cumulative effect of the studies. Additional univariate regression was performed for each outcome to evaluate the effects of age, gender and study quality as potential sources of heterogeneity, and results are summarized in Supplementary Material, Table S1. No significant associations were identified from this, apart from a significant effect of study randomization quality on post-bypass haematocrit levels.

Mortality

Mortality rates were reported by 5 studies, with no significant difference seen on combined analysis (OR 0.62, 95% CI 0.28 to 1.33, $P = 0.22$), and no heterogeneity detected (χ^2 = 0.50, I^2 = 0%, $P = 0.97$) (Fig. 2).

Post-bypass haematocrit

The post-bypass haematocrit levels were reported by 6 trials, comprising a total of 320 patients (Fig. 3). Meta-analysis of the pooled results showed significantly higher post-bypass haematocrit levels in the MUF group (mean difference 2.70, 95% CI 0.68–4.73, $P = 0.009$). There was significant heterogeneity in this analysis (χ^2 = 59.3, I^2 = 94.3%, $P < 0.001$).

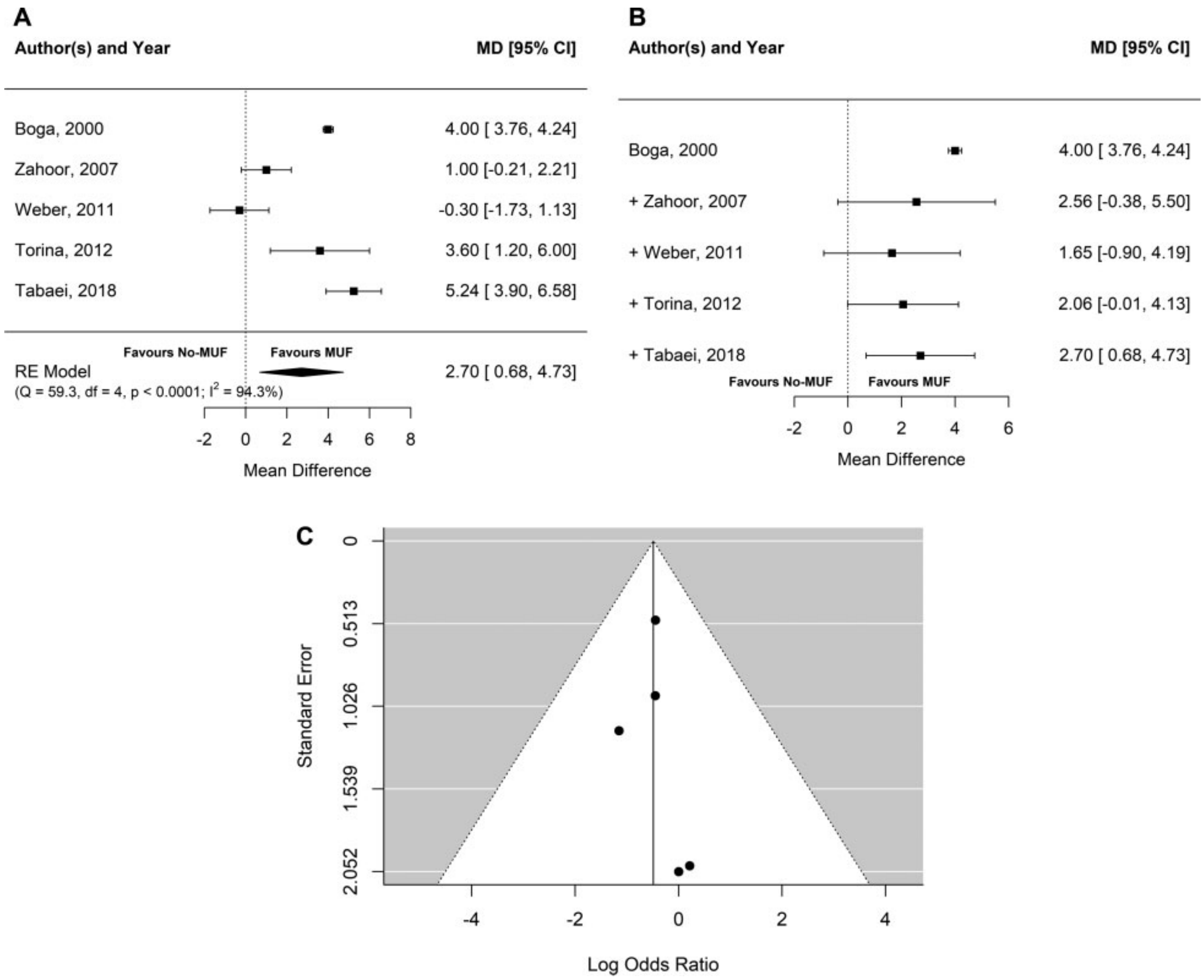


Figure 3: Meta-analysis outcomes for post-bypass haematocrit in MUF compared with no-MUF. (**A**) Non-cumulative meta-analysis, (**B**) cumulative meta-analysis, (**C**) funnel plot. MD: mean difference; CI: confidence interval; MUF: modified ultrafiltration; RE: random-effects.

Postoperative chest tube drainage

The postoperative chest tube drainage amount was reported by 10 studies, with a total of 1146 patients (Fig. 4). Combined meta-analysis revealed a significantly lower level of chest tube drainage in the MUF group (mean difference -105 ml, 95% CI -202 to -7 ml, $P = 0.032$). There was significant heterogeneity detected between trials (χ^2 = 85.0, I^2 = 87.5%, $P < 0.0001$).

Post-bypass blood transfusion

The post-bypass blood transfusion rate was available in 9 of the included studies, with a total of 1056 patients (Fig. 5). There was a significantly lower blood transfusion rate in the MUF group on meta-analysis (mean difference -0.73 units, 95% CI -0.98 to -0.47 units, $P < 0.0001$). There was a moderate degree of heterogeneity among trials (χ^2 = 19.8, I^2 = 59.8%, $P = 0.019$). Notably, the median number of red blood cell units used in the study by Weber *et al.* was higher than that seen in other studies (median 4 units in the MUF group, 5 units in the control group, compared to <3 units in other studies). This may be related to patient and surgical complexity, as this particular study focused on complex cardiac surgical cases.

Duration of intensive care unit stay

The postoperative duration of ICU stay was reported by 6 studies, with a total of 916 patients (Fig. 6). All of these studies reported a numerical trend towards shorter duration of ICU stay in the MUF group, without statistical significance. In this current meta-analysis, statistical significance was achieved on analysis of the pooled results, with shorter ICU stay in the MUF treatment group (mean difference -0.13 days, 95% CI -0.27 to -0.00 days, $P = 0.048$), and no heterogeneity detected (χ^2 = 1.89, I^2 = 0%, $P = 0.93$).

Duration of mechanical ventilation

The data for duration of postoperative mechanical ventilation were available in 3 of the included studies, comprising a total of 726 patients, in which the mean ventilation time was slightly over a day or less (Fig. 7). There was no statistically significant difference detected on meta-analysis (mean difference -0.47 h, 95% CI -2.05 to 1.12 h, $P = 0.56$), with no heterogeneity detected in this analysis (χ^2 = 1.77, I^2 = 0%, $P = 0.62$).

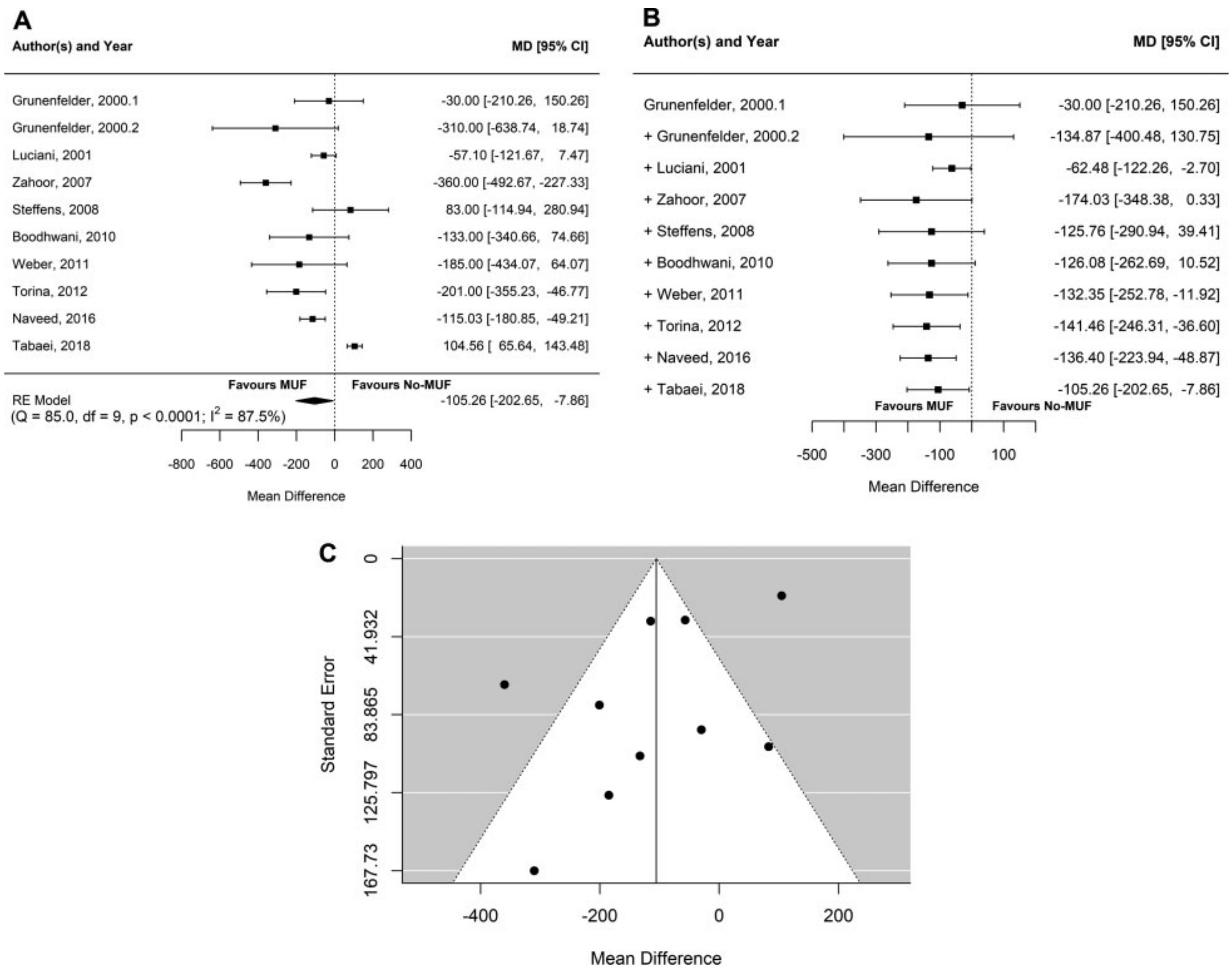


Figure 4: Meta-analysis outcomes for chest tube drainage in MUF compared with no-MUF (in ml). (**A**) Non-cumulative meta-analysis, (**B**) cumulative meta-analysis, (**C**) funnel plot. MD: mean difference; CI: confidence interval; MUF: modified ultrafiltration; RE: random-effects.

DISCUSSION

This study represents the first systematic review and meta-analysis of RCTs comparing MUF versus no-MUF in adult cardiac surgical patients. Significant results were found in several important clinical outcomes, including significantly improved postoperative haematocrit, and significantly reduced postoperative chest tube blood loss, blood transfusions and shorter duration of ICU stay after MUF was performed. The duration of postoperative mechanical ventilation was not significantly affected by MUF. There was no difference in mortality rates. These findings have a significant impact in the context of our current and future practice of cardiac surgery, and suggest that MUF, conventionally used more routinely in paediatric cardiac surgery, should be considered for incorporation into routine adult cardiac surgeries as well.

Effects of modified ultrafiltration in high-risk patient groups

The hypothesis that these beneficial effects of MUF may be especially important in high-risk patient categories such as older adult cardiac patients, patients with multiple pre-existing comorbidities, those undergoing complex surgeries or long CPB duration needs to be further elucidated in further prospective and larger volume studies to allow for more meaningful subgroup multivariate analysis. Out of the 13 RCTs included in this present study, Weber and Papadopoulos *et al.* focused on older adult patients undergoing complex cardiac surgery, with inclusion criteria of age >65 years, and complex procedures such as combined procedures, double-valve surgery, aortic surgery and re-do procedures. In these high-risk patients, the effect size of the reduction in chest tube bleeding after MUF was 80 ml more than the overall mean difference. Similarly, the effect size of the reduction in ICU stay was 0.47 days more than the mean difference. Accepting the possibility of confounders and heterogeneity between studies, future dedicated studies are needed to explore this effect and to determine if risk stratification will allow us to meaningfully decide which patients will benefit more from MUF during adult cardiac surgery. Most of the other studies consisted mostly or entirely of patients undergoing coronary artery bypass grafting, and this heterogeneity between studies must be taken into consideration during interpretation of the meta-analysis results.

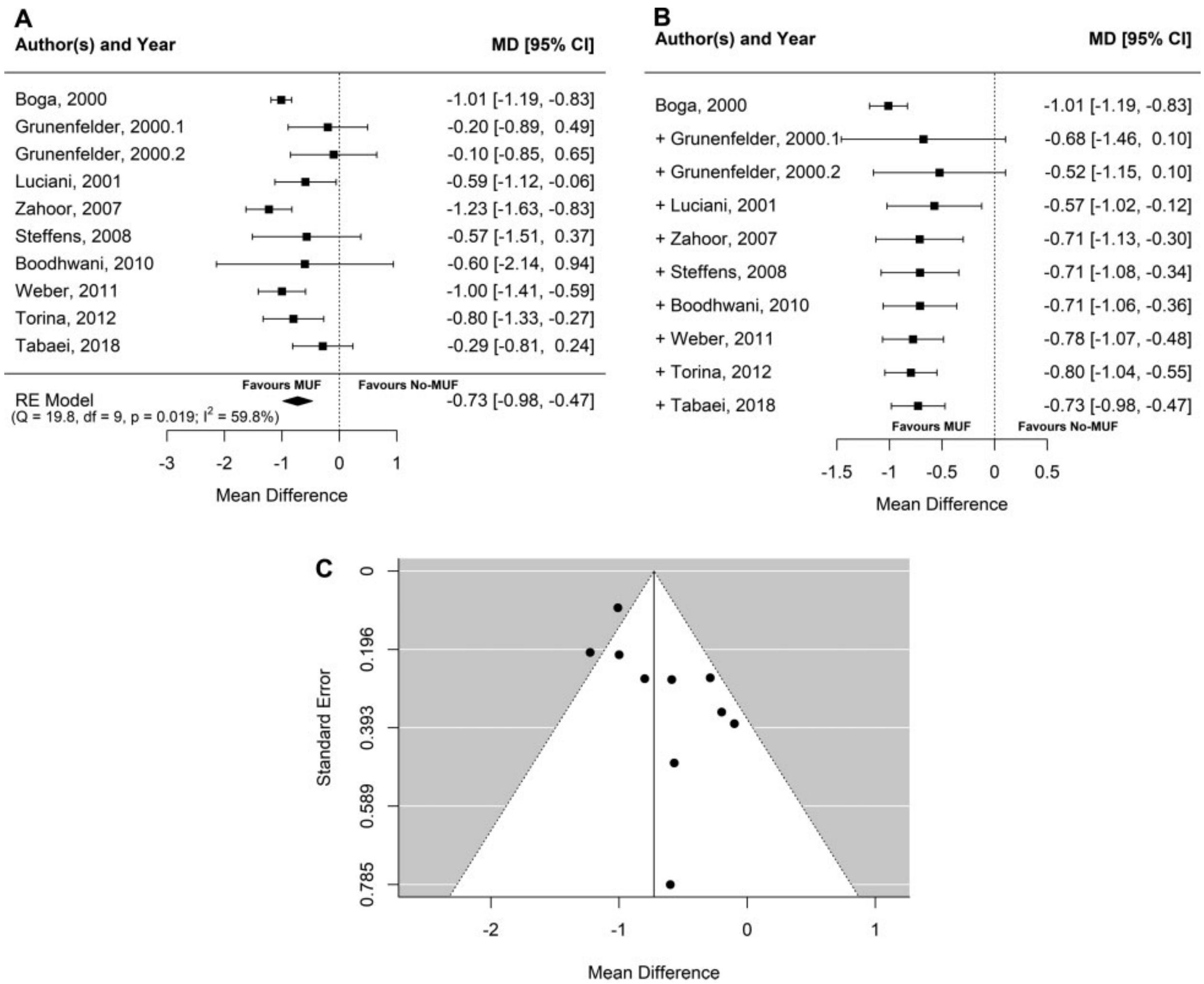


Figure 5: Meta-analysis outcomes for postoperative blood transfusions in MUF compared with no-MUF (in units). (**A**) Non-cumulative meta-analysis, (**B**) cumulative meta-analysis, (**C**) Funnel plot. MD: mean difference; CI: confidence interval; MUF: modified ultrafiltration; RE: random-effects.

Effects on modified ultrafiltration on coagulation, postoperative blood loss and inflammation

Our meta-analysis concluded that MUF significantly improved postoperative haematocrit and reduced postoperative chest tube blood loss and transfusion requirements, which is a reflection of the beneficial effects of MUF in reversing CPB-related coagulopathy. Previous studies have demonstrated increased concentrations of high-molecular weight substances including coagulation factors VII and X, platelet levels, platelet-factor 4 and antithrombin III after MUF [38, 39]. Weber *et al.* demonstrated significantly higher platelet aggregation on platelet function assays measured with multiple electrode aggregometry after MUF, without differences in thromboelastometric parameters and conventional laboratory coagulation analyses. This improvement in platelet aggregation may play a prominent role in the reduction of postoperative bleeding, as it has been speculated that CPB-related platelet activation and subsequent platelet dysfunction are a principle cause of post-CPB bleeding diathesis [3]. During CPB, platelet activation may be induced by mechanical trauma, heparin or hypothermia, following which there is degranulation of α-granules and increased surface expression of P-selectin [40]. Torina *et al.* described steady P-selectin levels measured throughout the observation period, suggesting that the process of MUF does not induce further platelet activation or dysfunction beyond what might have occurred as a result of CPB, despite an increased duration of time in contact with the synthetic circuit during MUF.

Similarly, Leyh *et al.* found reduced postoperative blood loss and transfusion requirements after MUF without differences in routine clotting test measurements (including platelet count, platelet-factor 4, activated partial thromboplastin time and fibrinogen levels), apart from significantly higher antithrombin III activity which persisted 24 h postoperatively. Antithrombin III has been shown to exhibit anti-inflammatory action independent of its thrombin-dependent activity, including the inhibition of tissue factor and down-regulation of proinflammatory cytokines [41].

It has been suggested that the reduced postoperative bleeding after hemofiltration is unlikely to be explained solely by haemoconcentration alone, and may be related to the removal of inflammatory mediators during hemofiltration, including cytokines and soluble adhesion molecules [42]. This has been reported in several previous studies demonstrating reduced plasma levels of tumour necrosis factor-α, interleukin-6 and interleukin-8 after ultrafiltration [24, 43, 44]. Grunenfelder *et al.* similarly

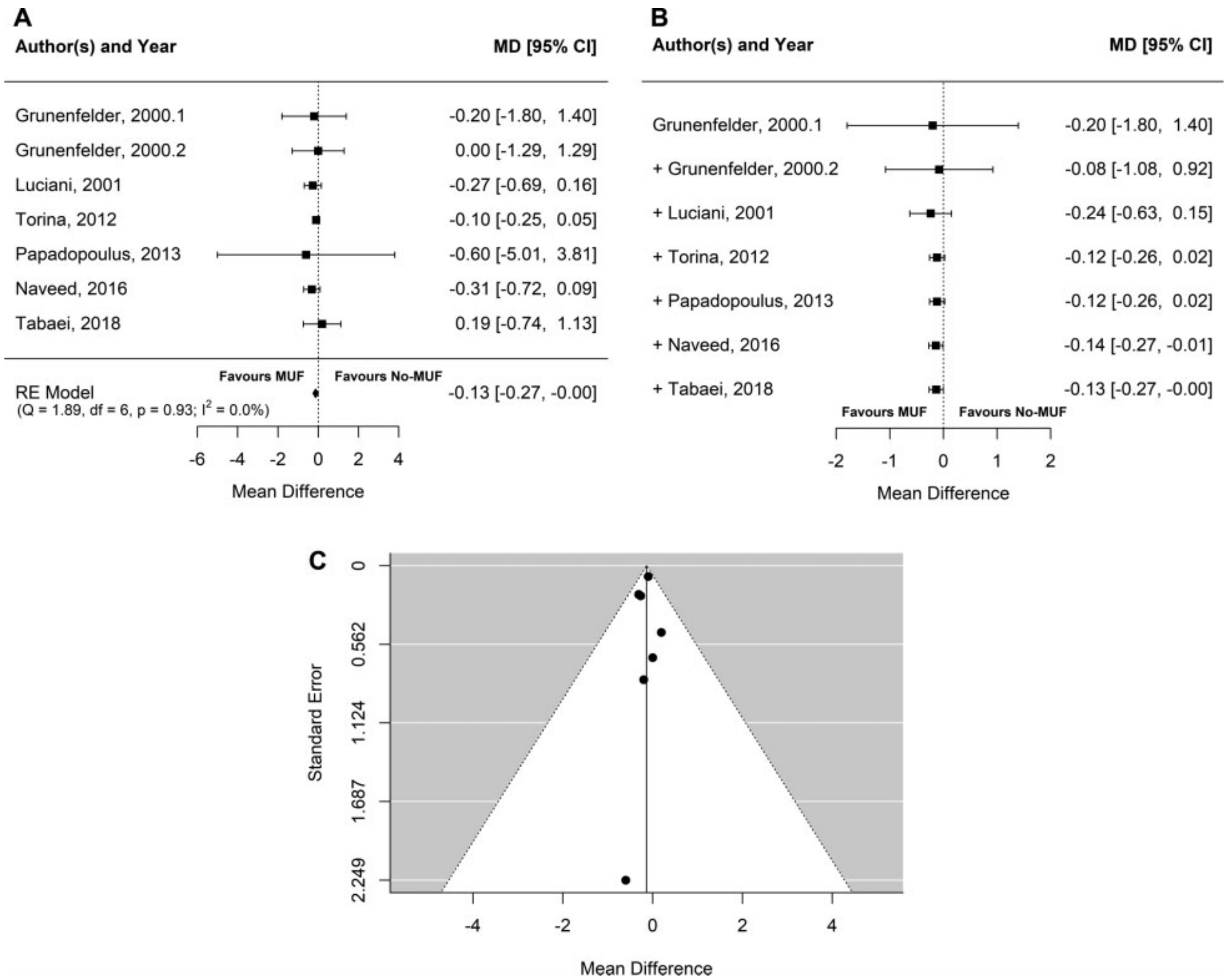


Figure 6: Meta-analysis outcomes for duration of ICU stay in MUF compared with no-MUF (in days). (**A**) Non-cumulative meta-analysis, (**B**) cumulative meta-analysis, (**C**) funnel plot. MD: mean difference; CI: confidence interval; MUF: modified ultrafiltration; RE: random-effects.

demonstrated a significant reduction in cytokine (tumour necrosis factor-α, interleukin-6, interleukin-8) and adhesion molecule levels (soluble E-selectin, soluble intercellular adhesion molecule-1) after MUF, particularly with hypothermic CPB. The interaction between these pro-inflammatory cytokines and the coagulation system occurs mainly along the tissue factor–factor VIIa extrinsic pathway via activation of vascular endothelial cells, which can subsequently express adhesion molecules and growth factors, contributing to both the inflammatory and coagulation pathways [45].

Consequent to the reduced postoperative blood loss and improved haematocrit, the reduction in transfusion requirements is an important finding supportive of the use of MUF in adult cardiac patients, with a considerably significant effect size seen on combined meta-analysis (mean of 0.73 less units used in MUF patients postoperatively). Balancing the costs of MUF with the costs and scarcity of blood transfusions is an important consideration pertaining to the health economics of this issue, along with the not-negligible risks of transfusion-related viral infections and transfusion reactions. Comparatively, MUF has been demonstrated to be a safe and feasible treatment option, and none of the studies in this meta-analysis reported any technical complications or cardiovascular sequelae after MUF was performed.

Effects of modified ultrafiltration on intensive care unit stay and pulmonary function

Our meta-analysis demonstrated a statistically significant reduction in ICU duration of stay, with a mean reduction of 0.13 days. Although of limited effect size, the statistical significance of the combined analysis is promising. Papadopoulos *et al.* reported a numerical trend towards shorter ICU stay in MUF patients, along with reduced tumour necrosis factor-α and interleukin-6, lower incidence of SIRS, lower requirement for vasopressors 12 h postoperatively, and significantly lower lactate concentrations 12 h postoperatively in MUF patients. This suggests that the inflammatory down-regulatory effects of hemofiltration can translate into observable clinical outcomes on larger pooled analyses. The incidence of SIRS was not consistently reported by the other studies in this meta-analysis, hence limiting our ability to draw more definitive conclusions on this particular complication. Importantly, none of the studies provided definitions for ICU discharge criteria, and differing institutional protocols in different centres might undermine any measurable differences in outcomes.

The lack of difference in postoperative duration of ventilation is counter-intuitive, given the theoretical advantages of MUF in improving pulmonary function. These include the filtration of excess water and circulating inflammatory mediators, which reduce

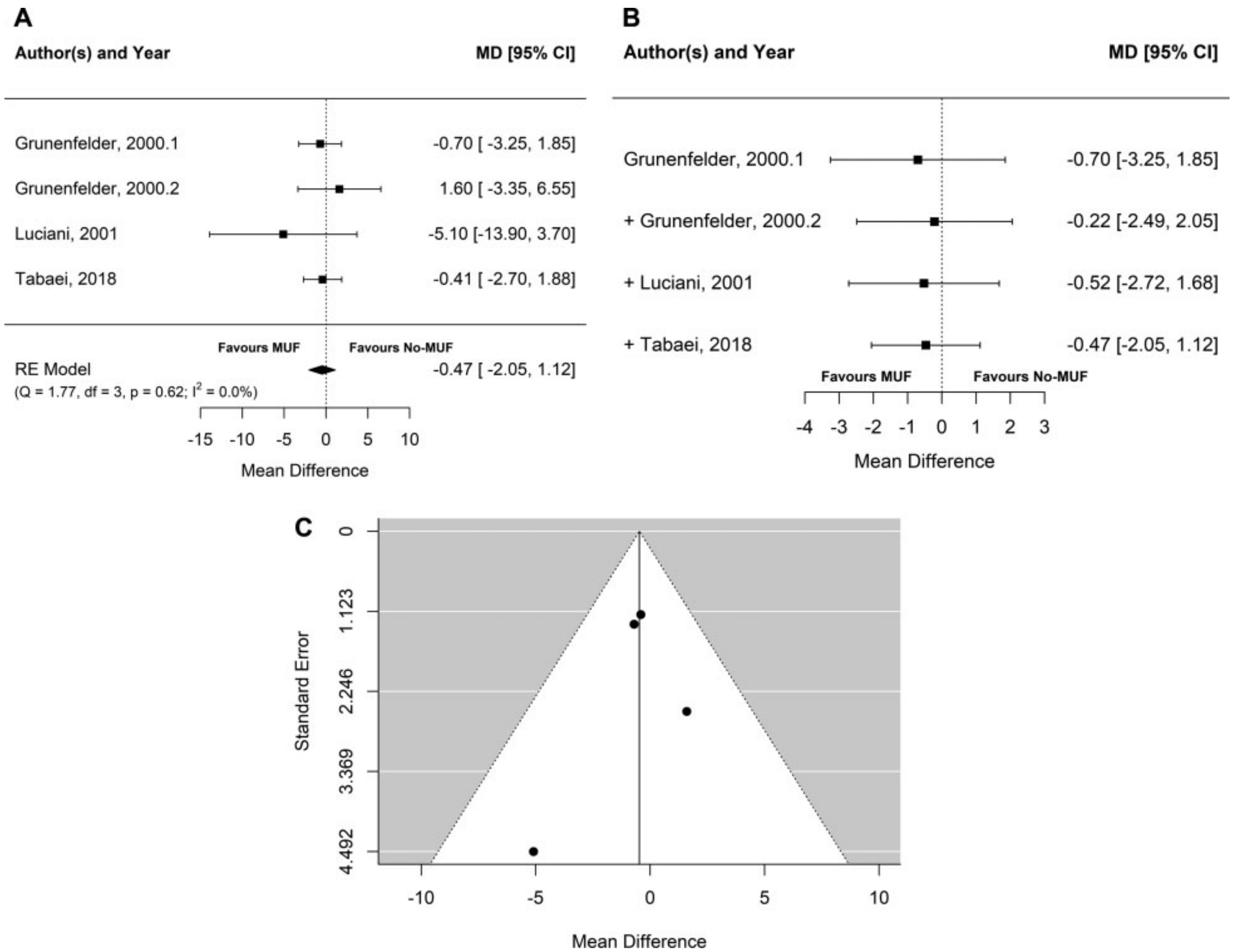


Figure 7: Meta-analysis outcomes for duration of mechanical ventilation in MUF compared with no-MUF (in hours). (**A**) Non-cumulative meta-analysis, (**B**) cumulative meta-analysis, (**C**) funnel plot. MD: mean difference; CI: confidence interval; MUF: modified ultrafiltration; RE: random-effects.

downstream effects of pulmonary oedema, cytokine-mediated pulmonary vascular barrier dysfunction and SIRS activation [3]. The interpretation of this outcome is limited by sample size, as only 3 studies included ventilation times for analysis. These studies also consist of mostly routine coronary artery bypass graft cases, and do not form a representative sample of more complex cases in which these pulmonary complications may become more consequential and produce a more pronounced effect on duration of ventilation. Nevertheless, Luciani *et al.* found a significantly lower incidence of respiratory complications after MUF, including less cases of respiratory failure and no cases of acute respiratory distress syndrome, with no significant differences in rates of pneumonia and pneumothorax. The use of ventilation time as an arbitrary measure of postoperative pulmonary function has also been questioned [17, 28], given the diverse spectrum of pathophysiological factors that contribute to pulmonary dysfunction including degree of oxygenation, compliance and vascular resistance—which may range from subclinical changes to overt acute respiratory distress syndrome. Paediatric studies have demonstrated improved pulmonary function after MUF in terms of improved pulmonary compliance, arterial oxygenation, alveolar–arterial oxygen gradient and pulmonary vascular resistance [42, 46–48]. Furthermore, 2 of these paediatric studies [47, 48] suggested that the improved pulmonary function post-MUF may be temporary, not lasting beyond 6 h postoperatively and without longer lasting effects on ventilation times and clinical outcomes. Further studies in adult populations measuring similar specific pulmonary parameters are needed to further elucidate this relationship.

Limitations

There was significant heterogeneity between studies, with high I^2 values seen in the meta-analysis of post-bypass haematocrit and chest tube drainage, which must be taken into consideration in the interpretation of these results. Factors that contribute to study heterogeneity include different patient characteristics, procedure types, CPB variables, complexity of surgery and different institutional protocols such as transfusion thresholds and ICU discharge criteria. The studies were also of mixed quality as assessed by the Jadad scale, with 5 out of 13 studies only scoring 1 point for methodology, while the rest scored 2 or more points. There was also disparity in the sample sizes of the studies, with all studies but one containing less than 100 patients. In view of this, cumulative meta-analysis in order of sample size was performed, which found significant results even after the largest study was excluded. We also accept a possibility of publication bias, as only English-language journal articles were included, and it is plausible that studies with positive findings tend to be published more than those with equivocal findings, which may inadvertently overestimate the treatment effect measured. In the funnel plot analysis, with the exception of the haematocrit funnel plot, the majority of the results lie within the expected 95% CI.

CONCLUSION

In conclusion, MUF has been proven to be a safe and feasible option in adult cardiac patients, with significant benefits including improved postoperative haematocrit, reduced postoperative chest tube bleeding, transfusion requirements and duration of ICU stay. These findings support the use of MUF in adult cardiac surgeries with CPB, although larger future prospective studies are required to validate these recommendations.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

ACKNOWLEDGEMENTS

We thank Suei Nee Wong (Senior Librarian, Medical Library, Centre for Translational Medicine, National University of Singapore) for her assistance with the electronic literature search strategy.

Conflict of interest: none declared.

Author contributions

Zhao Kai Low: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing—original draft; Writing—review & editing. **Fei Gao:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Writing—original draft; Writing—review & editing. **Kenny Yoong Kong Sin:** Data curation; Project administration; Resources; Supervision. **Kok Hooi Yap:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Giovanni Nicholas D. Andersen, Battista Luciani and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Besser M, Klein A. The coagulopathy of cardiopulmonary bypass. Crit Rev Clin Lab Sci 2010;47:197–212.
[2] Bronicki R, Hall M. Cardiopulmonary bypass-induced inflammatory response. Pediatr Crit Care Med 2016;17:S272–8.
[3] Paparella D, Yau T, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232–44.
[4] de Mendonça-Filho H, Pereira K, Fontes M, Vieira D, de Mendonça M, Campos L *et al.* Circulating inflammatory mediators and organ dysfunction after cardiovascular surgery with cardiopulmonary bypass: a prospective observational study. Crit Care 2006;10:R46.
[5] Boodhwani M, Williams K, Babaev A, Gill G, Saleem N, Rubens F. Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg 2006;30:892–7.
[6] Searles B. Ultrafiltration techniques and CPB: what we know and what we think we know. J Extra Corpor Technol 2006;38:64–5.
[7] Mongero L, Stammers A, Tesdahl E, Stasko A, Weinstein S. The effect of ultrafiltration on end-cardiopulmonary bypass hematocrit during cardiac surgery. Perfusion 2018;33:367–74.
[8] Thapmongkol S, Masaratana P, Subtaweesin T, Sayasathid J, Thatsakorn K, Namchaisiri J. The effects of modified ultrafiltration on clinical outcomes of adult and pediatric cardiac surgery. Asian Biomed 2015;9: 591–9.
[9] Chew M. Does modified ultrafiltration reduce the systemic inflammatory response to cardiac surgery with cardiopulmonary bypass? Perfusion 2004;19:S57–60.
[10] Alizadehasl A, Ziyaeifard M, Massoumi G. Modified ultrafiltration during cardiopulmonary bypass and postoperative course of pediatric cardiac surgery. Res Cardiovasc Med 2014;3:5.
[11] Daggett C, Lodge A, Scarborough J, Chai P, Jaggers J, Ungerleider R. Modified ultrafiltration versus conventional ultrafiltration: a randomized prospective study in neonatal piglets. J Thorac Cardiovasc Surg 1998; 115:336–42.
[12] Williams G, Ramamoorthy C, Chu L, Hammer G, Kamra K, Boltz M *et al.* Modified and conventional ultrafiltration during pediatric cardiac surgery: clinical outcomes compared. J Thorac Cardiovasc Surg 2006;132:1291–8.
[13] Thompson L, McElhinney D, Findlay P, Miller-Hance W, Chen M, Minami M *et al.* A prospective randomized study comparing volume-standardized modified and conventional ultrafiltration in pediatric cardiac surgery. J Thorac Cardiovasc Surg 2001;122:220–8.
[14] Davies M, Nguyen K, Gaynor J, Elliott M. Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1998;12:604.
[15] Chaturvedi R, Shore D, White P, Scallan M, Gothard J, Redington A *et al.* Modified ultrafiltration improves global left ventricular systolic function after open-heart surgery in infants and children. Eur J Cardiothorac Surg 1999;15:742–6.
[16] Finn A, Naik S, Klein N, Levinsky R, Strobel S, Elliott M. Interleukin-8 release and neutrophil degranulation after pediatric cardiopulmonary bypass. J Thorac Cardiovasc Surg 1993;105:234–41.
[17] Kuratani N, Bunsangjaroen P, Srimueang T, Masaki E, Suzuki T, Katogi T. Modified versus conventional ultrafiltration in pediatric cardiac surgery: a meta-analysis of randomized controlled trials comparing clinical outcome parameters. J Thorac Cardiovasc Surg 2011;142:861–7.
[18] Groom RC, Froebe S, Martin J, Manfra MJ, Cormack JE, Morse C *et al.* Update on pediatric perfusion practice in North America: 2005 survey. J Extra Corpor Technol 2005;37:343–50.
[19] Friedrich I, Simm A, Kötting J, Thölen F, Fischer B, Silber R. Cardiac surgery in the elderly patient. Deutsches Aerzteblatt Online 2009;106: 416–22.
[20] Nicolini F, Agostinelli A, Vezzani A, Manca T, Benassi F, Molardi A *et al.* The evolution of cardiovascular surgery in elderly patient: a review of current options and outcomes. BioMed Res Int 2014;2014:736298.
[21] Rong LQ, Di Franco A, Gaudino M. Acute respiratory distress syndrome after cardiac surgery. J Thorac Dis 2016;8:E1177–86.
[22] Alexander K, Anstrom K, Muhlbaier L, Grosswald R, Smith P, Jones R *et al.* Outcomes of cardiac surgery in patients age ≥80 years: results from the National Cardiovascular Network. J Am Coll Cardiol 2000;35:731–8.
[23] Jae HC, Dong HK, Jung KJ, Seung WL. Assessing the quality of randomized controlled trials published in the Journal of Korean Medical Science from 1986 to 2011. J Korean Med Sci 2012;27:973–80.
[24] Viechtbauer W. Conducting meta-analyses in R with the metaphor package. J Stat Softw 2010;36:1–48.
[25] Onoe M, Magara T, Yamamoto Y, Nojima T. Modified ultrafiltration removes serum interleukin-8 in adult cardiac surgery. Perfusion 2001;16: 37–42.
[26] Grünenfelder J, Zünd G, Schoeberlein A, Maly FE, Schurr U, Guntli S *et al.* Modified ultrafiltration lowers adhesion molecule and cytokine levels after cardiopulmonary bypass without clinical relevance in adults. Eur J Cardiothorac Surg 2000;17:77–83.
[27] Bog'a M, Islamog'lu F, Badak I, Çikirikçiog'lu M, Bakalim T, Yag'di T *et al.* The effects of modified hemofiltration on inflammatory mediators and cardiac performance in coronary artery bypass grafting. Perfusion 2000; 15:143–50.

[28] Leyh RG, Bartels C, Joubert-Hübner E, Bechtel JF, Sievers HH. Influence of modified ultrafiltration on coagulation, fibrinolysis and blood loss in adult cardiac surgery. Eur J Cardiothorac Surg 2001;19:145–51.
[29] Luciani GB, Menon T, Vecchi B, Auriemma S, Mazzucco A. Modified ultrafiltration reduces morbidity after adult cardiac operations. Circulation 2001;104:I253–9.
[30] Zahoor M, Abbass S, Khan AA, Ahmad SA. Modified ultrafiltration: role in adult cardiac surgical haemostasis. J Ayub Med Coll Abbottabad 2007; 19:49–54.
[31] Steffens TG, Kohmoto T, Edwards N, Wolman RL, Holt DW. Effects of modified ultrafiltration on coagulation as measured by the thromboelastograph. J Extra Corpor Technol 2008;40:229–33.
[32] Boodhwani M, Hamilton A, Varennes BD, Mesana T, Williams K, Wells GA *et al.* A multicenter randomized controlled trial to assess the feasibility of testing modified ultrafiltration as a blood conservation technology in cardiac surgery. J Thorac Cardiovasc Surg 2010;139:701–6.
[33] Weber CF, Jámbor C, Strasser C, Moritz A, Papadopoulos N, Zacharowski K *et al.* Normovolemic modified ultrafiltration is associated with better preserved platelet function and less postoperative blood loss in patients undergoing complex cardiac surgery: a randomized and controlled study. J Thorac Cardiovasc Surg 2011;141:1298–304.
[34] Torina AG, Silveira-Filho LM, Vilarinho KA, Eghtesady P, Oliveira PP, Sposito AC *et al.* Use of modified ultrafiltration in adults undergoing coronary artery bypass grafting is associated with inflammatory modulation and less postoperative blood loss: a randomized and controlled study. J Thorac Cardiovasc Surg 2012;144:663–70.
[35] Papadopoulos N, Bakhtiary F, Grün V, Weber C, Strasser C, Moritz A. The effect of normovolemic modified ultrafiltration on inflammatory mediators, endotoxins, terminal complement complexes and clinical outcome in high-risk cardiac surgery patients. Perfusion 2013;28:306–14.
[36] Naveed D, Khan RA, Malik A, Shah SZA, Ullah I, Hussain A. Role of modified ultrafiltration in adult cardiac surgery: a prospective randomized control trial. J Ayub Med Coll Abbottabad 2016;28:22–5.
[37] Tabaei AS, Mortazian M, Yaghoubi A, Gorjipour F, Manesh SA, Totonchi Z *et al.* Modified ultrafiltration in coronary artery bypass grafting: a randomized, double-blinded, controlled clinical trial. Iran Red Crescent Med J 2018;20:e66187.
[38] Fujita M, Ishihara M, Kusama Y, Shimizu M, Kimura T, Iizuka Y *et al.* Effect of modified ultrafiltration on inflammatory mediators, coagulation factors, and other proteins in blood after an extracorporeal circuit. Artif Organs 2004;28:310–3.
[39] Kiziltepe U, Uysalel A, Corapcioglu T, Dalva K, Akan H, Akalin H. Effects of combined conventional and modified ultrafiltration in adult patients. Ann Thorac Surg 2001;71:684–93.
[40] Wahba A, Rothe G, Lodes H, Barlage S, Schmitz G, Birnbaum D. Effects of extracorporeal circulation and heparin on the phenotype of platelet surface antigens following heart surgery. Thromb Res 2000;97:379–86.
[41] Souter P, Thomas S, Hubbard A, Poole S, Römisch J, Gray E. Antithrombin inhibits lipopolysaccharide-induced tissue factor and interleukin-6 production by mononuclear cells, human umbilical vein endothelial cells, and whole blood. Crit Care Med 2001;29:134–9.
[42] Journois D, Pouard P, Greeley WJ, Mauriat P, Vouhé P, Safran D. Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery: effects on hemostasis, cytokines, and complement components. Anesthesiology 1994;81:1181–9.
[43] Wang M, Chiu I, Hsu C, Wang C, Lin P, Chang C *et al.* Efficacy of ultrafiltration in removing inflammatory mediators during pediatric cardiac operations. Ann Thorac Surg 1996;61:651–6.
[44] Millar A, Armstrong L, van der Linden J, Moat N, Ekroth R, Westwick J *et al.* Cytokine production and hemofiltration in children undergoing cardiopulmonary bypass. Ann Thorac Surg 1993;56: 1499–502.
[45] Levi M, Keller T, van Gorp E, ten Cate H. Infection and inflammation and the coagulation system. Cardiovasc Res 2003;60:26–39.
[46] Keenan H, Thiagarajan R, Stephens K, Williams G, Ramamoorthy C, Lupinetti F. Pulmonary function after modified venovenous ultrafiltration in infants: a prospective, randomized trial. J Thorac Cardiovasc Surg 2000;119:501–7.
[47] Onoe M, Oku H, Kitayama H, Matsumoto T, Kaneda T. Modified ultrafiltration may improve postoperative pulmonary function in children with a ventricular septal defect. Surg Today 2001;31:586–90.
[48] Mahmoud A, Burhani M, Hannef A, Jamjoom A, Al-Githmi I, Baslaim G. Effect of modified ultrafiltration on pulmonary function after cardiopulmonary bypass. Chest 2005;128:3447–53.