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Blood Purification and Mortality in Sepsis: A Meta-analysis of Randomized Trials

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Abstract

Objectives—Although blood purification improves outcomes in animal studies of sepsis, results of clinical trials have been mixed. We conducted a systematic review and meta-analysis of randomized trials to determine the association between various blood purification techniques and all-cause mortality in humans with sepsis.

Data Sources—We searched for relevant studies in MEDLINE, EMBASE, and the Cochrane Library database from January 1966 until May 2012.

Study Selection—Inclusion required a diagnosis of sepsis and comparison of blood purification techniques including hemofiltration, hemoperfusion, plasma exchange, or hemodialysis with no blood purification (control group).

Data Extraction—Two authors independently selected studies and extracted data. Summary statistics, risk ratios (RRs), and CIs were calculated using random-effects modeling. Study quality was assessed using Jadad score, and publication bias using funnel plots and Egger's statistic.

Data Synthesis—Overall, blood purification decreased mortality compared to no blood purification (35.7% versus 50.1%; RR, 0.69; 95% CI, 0.56–0.84; $p < 0.001$; 16 trials, n=827). However, these results were driven mainly by hemoperfusion (RR, 0.63; 95% CI, 0.50–0.80; $p < 0.001$; 10 trials, n=557), and plasma exchange (RR, 0.63; 95% CI, 0.42–0.96; $p = 0.03$; 2 trials, n=128). Pooling of all trials of blood purification for treatment of sepsis was no longer associated with lower mortality (RR, 0.89; 95% CI, 0.71–1.13; p = 0.36; 8 trials, n=457) after excluding trials using polymyxin B hemoperfusion.

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Conclusions—Blood purification techniques including hemoperfusion, plasma exchange, and hemofiltration with hemoperfusion were associated with lower mortality in patients with sepsis. These results were mainly influenced by studies using polymyxin B hemoperfusion from Japan.

Keywords

sepsis; blood purification; cytokines; inflammation; mortality; meta-analysis

INTRODUCTION

Severe sepsis, defined as sepsis with acute organ dysfunction, affects more than 750,000 people annually in the United States with a mortality rate ranging from 28% to 50% (1,2). With the recent removal of Xigris, the only FDA-approved treatment for sepsis, from the market due to failure to show a survival benefit for patients with septic shock (3), the medical community is urgently seeking a possible therapy. Source control and antibiotics remain the mainstays of therapy for infection (4) but no specific treatment is available for sepsis. Observations over more than 20 years have suggested a role for extracorporeal blood purification. However, no definitive trials have been published to date.

Sepsis involves complex interactions between endothelial cells, platelets, leukocytes, coagulation system, and multiple pro- and anti-inflammatory mediators, and often results in multiple organ dysfunction syndrome (MODS) leading to death (5,6). Since there are correlations between high concentrations of circulating inflammatory cytokines for patients with sepsis or septic shock (7–9) and since mortality is highest when both pro- and anti-inflammatory cytokine levels are high (7), extracorporeal blood purification is used by some centers in order to modulate the immune response. Unlike drugs targeting specific mediators, blood purification can influence a wide range of molecules.

Blood purification for sepsis has consisted of various techniques including high volume hemofiltration, high adsorption hemofiltration, high cut-off membrane hemofiltration, plasma exchange, and hybrid systems like coupled plasma filtration adsorption. Recently, the spectrum of techniques available for blood purification has been broadened further with technological advances particularly in the area of hemoperfusion. However, the use of blood purification is controversial and results vary among studies (9–17). No systematic reviews have pooled the available evidence from various types of blood purification compared to conventional therapy. Therefore we performed a systematic review and meta-analysis to attempt to determine whether blood purification decreases mortality in patients with sepsis so as to guide further research in this area.

MATERIALS AND METHODS

Selection of Studies

We reviewed MEDLINE and EMBASE citations between January 1, 1966, and May 1, 2012, and the Cochrane Central Register of Controlled Trials Library database through May 1, 2012. Search was performed using medical subject heading (MeSH) terms and text words with Boolean strategy, and cross-searching of the following 3 categories: (1) modality of blood purification (“hemofiltration” OR “renal replacement therapy” OR “blood purification” OR “dialysis” OR “hemoperfusion” OR “hemoadsorption” OR “plasmafiltration” OR “plasma exchange”); (2) disease (“sepsis” OR “infection” OR “septic shock” OR “systemic inflammatory response syndrome” OR “SIRS” OR “multiple organ dysfunction syndrome” OR “MODS”); and (3) others related (“outcome” OR “intensive care unit” OR “ICU” OR “critically ill patients” OR “mortality” OR “prognosis”).The limits were “human” and “English” language. We limited article types to randomized controlled

trials, and because sepsis in children is different in terms of infectious etiology and host response, we only included adults more than 18 years of age. The bibliographies of all relevant studies and recent review articles were scanned to identify additional citations.

We categorized trials according to the type of blood purification technique used. Studies using continuous or intermittent veno-venous hemofiltration, regardless of filtration rate, duration and frequency, were classified as "hemofiltration". Trials of a blood purification technique where a sorbent is placed in direct contact with blood in an extracorporeal circuit were considered to be "hemoperfusion", and trials that removed and replaced plasma were grouped as "plasma exchange". Conventional treatment was defined as the ordinary therapy (including fluid resuscitation, nutrition support, antibiotic therapy, and other organ support in the intensive care unit) but with no forms of extracorporeal treatment.

Quality Assessment

We assessed quality of each study included in the meta-analysis using the Jadad score (18), which assesses the conduct of randomization, concealment of treatment allocation, similarity of treatment groups at baseline, clinician blinding, and the description of withdrawals and dropouts. The Jadad score ranges from 1 (poor) to 5 (excellent) where RCT quality is high when scores are ≥3. The Jadad/Oxford quality scales require a double-blinded placebo for 2 of the 5 points. Due to the nature of the intervention and logistic reasons, none of the studies reported double-blinding. Thus we used "investigator blinding" for assessment of quality of studies included in this meta-analysis (18).

Data Abstraction and Clinical Outcome

Study selection and data abstraction was performed independently by two reviewers (FZ and ZP) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (19) and any discrepancies between reviewers were resolved by consensus. For each study raw data were extracted using a standard form, which included the first author, study design, year of publication, total number of patients, patient characteristics, details regarding the outcomes and types of sepsis. In addition, we also assessed the modality of blood purification, as well as the comparisons or related description of primary outcome between blood purification and conventional treatment, such as mortality or physiologic variables. The main endpoint was mortality as defined in the individual trials. If mortality was assessed at several time points in a study, we used data from the latest follow-up time for overall mortality assessment.

Statistical Analysis

For each trial, we derived the risk ratios (RRs) and 95% CIs of reported mortality in patients assigned to blood purification versus controls. Statistical heterogeneity among trials included in the meta-analysis was assessed and quantified using the I^2 Statistic, which estimates the percentage of total variation across studies due to heterogeneity rather than chance (20). Because the random effects model incorporates statistical heterogeneity and provides a more conservative estimate of the pooled effect size compared to the fixed model, we present the results of all analyses according to a random effects model by using the method of DerSimonian and Laird that considers both within study and between-study variation (21).

To further ascertain what factors may have influenced treatment effects, we performed a variety of sensitivity analyses to determine the RR of death within particular groups: mean patient age ≥ 60 years vs. age < 60 years; APACHE score ≥ 28 vs. < 28; sepsis, severe sepsis vs. septic shock; publication year ≥ 2005 vs. < 2005; Jadad score ≥ 3 vs. < 3. We assessed publication bias by evaluating the funnel plots (*i.e.*, plots of study results against

precision) and with Egger's statistic (22). Egger statistical analyses were performed using Stata version 10.0 (StataCorp, College Station,TX). Two-tailed $p < 0.05$ was considered statistically significant. All other statistical analyses were performed by using Review Manager, version 5.1.2 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Selection and Characteristics of Trials

Our initial search yielded 1717 studies (Fig. 1). After excluding 128 studies due to duplicate publication, we considered the abstracts of 1589 studies. After evaluating the abstract of each study, 1553 studies were excluded as they did not meet the inclusion criteria. Subsequently, we carefully read the full-text of each of the remaining 36 trials and excluded 20 trials: as they did not report comparison between blood purification and conventional treatment (n=15); enrolled patients without a diagnosis of sepsis (n=3) or did not report mortality (n=2).

Table 1 shows the characteristics of randomized trials. Ten single-center (9,17,23, 26,29–34) and six multicenter studies (24,25,27,28,35,36) were identified. These trials were reported between 1999 and 2010. The Country of origin in six studies is Japan (29,30,31,33,34,36), all of which reported on hemoperfusion (Table 1, Table 2). The mean age of the study participants ranged from 33 to 75 years; 637 (77%) patients were admitted to the ICU (17,24–29,31–33,35); and the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 24.2 (9,17,23,24,27–36). Patients with sepsis, severe sepsis or septic shock were diagnosed mainly according to the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference criteria (37).

Ten trials reported patients with either severe sepsis or septic shock, while five trials reported only patients with a diagnosis of sepsis. One trial included patients with sepsis, severe sepsis or septic shock (Table 1). The blood purification techniques used included hemoperfusion (10 trials), hemofiltration (4 trials), and plasma exchange (2 trials) (Table 2). Six trials included in our analysis reported the results of 28-day mortality and 4 trials reported results of hospital mortality. Two trials reported 28-day, hospital, and/or ICU mortality, and one trial reported 14-day mortality. There still had three trials in which mortality was reported but length of follow-up was not clearly stated (Table 2). All studies evaluated the effects between blood purification and conventional treatment in patients with sepsis using some primary clinical outcome such as survival, hemodynamics, or change in organ function (APACHE II /III score /SAPS II score/SOFA score) (Table 2).

Association of Blood Purification with Mortality

Overall mortality in 16 trials was 42.7%. Of the blood purification group, 35.7% of patients died compared to 50.1% in the conventional treatment group. Overall, blood purification techniques decreased mortality in patients with sepsis, severe sepsis or septic shock (RR, 0.69; 95% CI, 0.56–0.84; $p < 0.001$), including 28-day mortality (RR, 0.80; 95% CI, 0.64–0.99; $p = 0.04$) and hospital mortality (RR, 0.57; 95% CI, 0.44–0.75; $p < 0.001$) (Fig. 2). No significant heterogeneity was found ($Chi^2 = 20.54$, df = 15, $p = 0.15$; $I^2 = 27\%$) (Fig. 2).

Association of Blood Purification Modality with Mortality

We found that hemoperfusion (RR, 0.63; 95% CI, 0.50–0.80; $p < 0.001$; 10 trials, n=557; heterogeneity, $p = 0.15$) or plasma exchange (RR, 0.63; 95% CI, 0.42–0.96; $p = 0.03$; 2 trials, n=128; heterogeneity, $p = 0.80$) decreased mortality in patients with sepsis. However, we could not find a similar effect with hemofiltration alone (RR, 1.13; 95% CI, 0.75–1.71; $p = 0.56$; 4 trials; n = 142; heterogeneity, $p = 0.74$) (Fig. 3A). We also found that

hemoperfusion with polymyxin B (PMX-B) decreased mortality in patients with sepsis (RR, 0.57; 95% CI, 0.45–0.72; $p < 0.001$; 8 trials, n=370; heterogeneity, $p = 0.32$) while hemoperfusion without PMX-B (RR, 0.98; 95% CI, 0.66–1.47 ; $p = 0.94$; 2 trials, n=187; heterogeneity, $p = 0.44$), or pooling all blood purification studies without PMX-B (RR, 0.89; 95% CI, 0.71–1.13 ; $p = 0.36$; 8 trials, n=457; heterogeneity, $p = 0.55$) did not (Fig. 3B). When combined with hemoperfusion, hemofiltration was associated with greater benefit (RR, 0.69; 95% CI, 0.55–0.87; $p = 0.002$; 14 trials; n = 699; heterogeneity, $p = 0.09$) than hemofiltration alone. On the other hand, hemofiltration combined with plasma exchange did not affect the mortality (RR, 0.85; 95% CI, 0.63–1.14; $p = 0.28$; 6 trials; n = 270; heterogeneity, $p = 0.41$) (Fig. 3A). Studies conducted in Japan showed that blood purification decreased mortality in patients with sepsis (RR, 0.50; 95% CI, 0.36–0.70; $p < 0.001$; 6 trials; n = 271; heterogeneity, $p = 0.18$) while pool results from studies conducted in other countries were not significant (RR, 0.86; 95% CI, 0.69–1.06; $p = 0.16$; 10 trials; n = 556; heterogeneity, $p = 0.58$) (Fig. 3B).

Sensitivity Analyses of Association between Blood Purification and Mortality

We conducted sensitivity analyses by stratifying our analysis by various subgroups known to influence outcome from sepsis (Table 3). We found no significant differences in effect when trials were stratified by mean age (≥ 60 versus < 60 years) and mean APACHE II score (≥ 28 versus < 28) at enrollment. However, blood purification appeared to have a greater effect on mortality in trials enrolling patients with sepsis (RR, 0.40; 95% CI, 0.26–0.64; $p < 0.001$; 5 trials, n=140) compared to those enrolling patients with severe sepsis or septic shock (RR, 0.79; 95% CI, 0.62–1.00; $p = 0.05$; 10 trials, n=589), and the p value for interaction between these two groups was 0.01 (Table 3). Similar results could be seen in effect when trials were stratified by publication year ($p = 0.04$) (Table 3). Study quality (Jadad score ≥ 3 or < 3) did not affect the results ($p = 0.64$). We also conducted sensitivity analyses restricted to hemoperfusion studies by stratifying mean age (≥ 60 versus < 60 years), mean APACHE II score (≥ 28 versus < 28) at enrollment, or publication year (before 2005 versus 2005 and later). The results were consistent with the findings with all "purification techniques" except for publication year ($p = 0.28$) (Table 3).

Adverse Effects

There were few clinically important adverse effects related to blood purification. Two trials reported immediate adverse events, which were considered to be possibly device related (fever) during hemoperfusion treatment (23,27). Cruz et al (24) reported some adverse reactions, including cartridge clotting (4 cases, 6%), hypotension (1 case, 1.5%) and tachycardia (2 cases, 3%). Busund et al (32) reported that six patients had episodes of hypotension during the plasmapheresis procedure, and one patient had a reaction to fresh-frozen plasma.

Quality of Studies and Publication Bias

All trials included in the meta-analysis were randomized and have been published in full manuscript form. The mean Jadad score was 2.75 for studies included in our analysis (using investigator-blinding for double-blinding). Seven trials had a Jadad score ≥ 3, while 9 trials received a score of 2 or less (Table 1). No evidence of publication bias was detected for RR of death by either funnel plots or Egger test ($p = 0.14$) (Fig. 4A, 4B).

DISCUSSION

We found evidence that blood purification using hemoperfusion, plasma exchange, and hemofiltration combined with hemoperfusion was significantly associated with a decrease in mortality among patients with sepsis, severe sepsis or septic shock. Thus, further

development of blood purification strategies for management of sepsis would seem warranted.

Early clinical and experimental studies in blood purification for sepsis focused on methods used for treatment of renal failure, especially continuous veno-venous hemofiltration (CVVH) (15,38,39). Often these trials used standard “renal dose” intensities although more recently, so-called high-volume hemofiltration has been advocated (9–11,15–16). Meanwhile, large multi-centered clinical trials have revealed that increasing intensity of renal replacement therapy beyond conventionally recommended doses does not improve patient survival (40,41). Subgroup analysis in these trials also does not support an advantage for higher intensity in patients with renal failure and sepsis. This may be because conventional renal replacement therapy is not able to affect changes in soluble inflammatory mediators (17,25) and thus alternative techniques are needed if blood purification is to result in improved survival for patients with sepsis.

Importantly however, the exact targets for blood purification in sepsis are unknown. We recently demonstrated in rodents that acute changes in the usual sepsis mediators were not necessary to impact survival using hemoperfusion (42). Indeed, it is increasingly recognized that death from sepsis (or perhaps critical illness in general) may be more a function of immune suppression than of cytotoxic inflammation (43). Therefore, the targets of immune modulation may be immune suppressive factors, immune effector cells, or perhaps, chemokine gradients.

Alternatives to standard hemofiltration such as high-adsorption CVVH appear more effective for reducing plasma cytokine concentrations in patients with septic shock as well as for impacting physiologic outcomes such as decreasing norepinephrine requirements (12). However, other modalities such as hemoperfusion and plasma exchange are now being examined more closely. For example, hemoperfusion with a Polymyxin B fiber column appears to improve survival compared with conventional treatment (24,29,30,33,34,36). Trials included in this meta-analysis varied in terms of blood purification modality, and reflected the diversity of clinical practice informing trial methodology. Interestingly, our results were reasonably consistent across various forms of blood purification without significant heterogeneity. Likewise, the risk of publication bias was low, though not impossible given limitations of the Eggers statistic.

A surprising finding of our analysis shown in table 3 was the fact that the impact of blood purification on survival was not attenuated in subgroups with lower risk of death (age < 60, APACHE II score < 28, non-severe sepsis). This finding may be of particular importance because many sepsis trials have focused on patients with severe disease (9,17,23–25,27–29,32,36). One consequence of this approach is that patients tend to be enrolled late in the course of sepsis, perhaps when therapies are less likely to be effective. Concern over this strategy is further heightened when one appreciates that preclinical models are often based on early treatment or even pretreatment in animals (39,42). Future trials of blood purification may need to consider this aspect more carefully.

Similarly, older patients have an increased risk of death and shorter survival time in studies of sepsis (44). However, we could not demonstrate any difference in the effect of blood purification in patients < 60 years of age compared to older patients. In a cohort study, Brar et al reported that individuals with acute renal failure over 50 who were treated with continuous renal replacement therapy had a lower mortality (22%) than their younger counterparts (50%) (45).

Some investigators have sought to examine combination therapy using different blood purification techniques in patients with sepsis or septic shock (14,46). For example,

Yonekawa et al (47) reported that patients with severe sepsis responded to treatment combining continuous endotoxin apheresis and hemodiafiltration. Too few trials are available to examine this approach. However, given the inherent differences in the various blood purification techniques on specific variables of interest in sepsis (e.g. endotoxin, cytokines, cells), combined therapy does seem appealing.

We found no evidence that study quality of the trials included affected our results. Although there were significant differences in effect when trials were stratified by publication year ($p = 0.04$), we did not find evidence for this effect when the analysis was restricted to hemoperfusion ($p = 0.28$). However, there are still important limitations to this report. First, and foremost, studies were small (most less than 80 subjects and none greater than 150) and overall quality was modest (mean Jadad score 2.75). The risk of false attribution of positive effect from pooling small trials is well known (48). Thus, we do not believe that these results constitute a reason to change clinical practice but rather support the need for further research, particularly given the dismal state of affairs in the area of sepsis therapeutics (3). However, we also note significant regional differences in the management of sepsis and the reality that blood purification is commonly used in some and unknown in other places around the world (49). Second, there was no standard reporting for survival and different authors chose different endpoints. Therefore it was not possible to use a single mortality endpoint (hospital, 28 day etc.) across trials. Patient-level data were not available for the majority of trials so we did not attempt to perform a patient-level analysis. Third, due to the nature of the intervention and for logistic reasons, studies were not double-blinded. Although we used “investigator blinding” for assessment of quality of studies included in this meta-analysis (18), there is still potential for bias. Similarly, underreporting of the adverse effects associated with blood purification is possible, especially since there are no standards for adverse effect reporting, and none of the studies included in the meta-analysis had a systematic approach to safety data collection and reporting.

Finally, we acknowledge that sepsis is a complex disease and blood purification is a complex intervention. The effectiveness of blood purification might be influenced by the unique constellation of treatments that are used for and epidemiology of sepsis at individual centers and may not be generalizable. For example, blood purification has the potential to impact plasma drug concentrations including antibiotics (50). It is possible therefore that blood purification might have different effects when used in conjunction with antibiotics that depend on time-dependent kinetics compared to peak concentration-dependent kinetics (50). Since selection of antibiotics is at least partially influenced by treating center, it is reasonable to hypothesize variable effects of blood purification across centers, all other factors aside. Similarly, our results suggest that the main drivers for the beneficial effects of blood purification in this analysis come from studies of hemoperfusion with PMX-B, and were performed in a single country (29,30,31,33,34,36). Although the overall effects of blood purification without PMX-B were consistent with PMX-B studies ($p = 0.15$; $I^2 = 27\%$) the effect size is considerably smaller (RR 0.89 vs. 0.57) and fails to reach statistical significance. Thus, much additional work is needed. However, our results suggest a likely role for this form a treatment in a disease that has, so far, eluded effective therapy.

CONCLUSION

In conclusion, pooled results of multiple small studies of moderate study quality show that blood purification (including hemoperfusion or plasma exchange alone, hemofiltration combined with hemoperfusion) is associated with lower mortality in patients with sepsis. These results were mainly influenced by studies using hemoperfusion with PMX-B.

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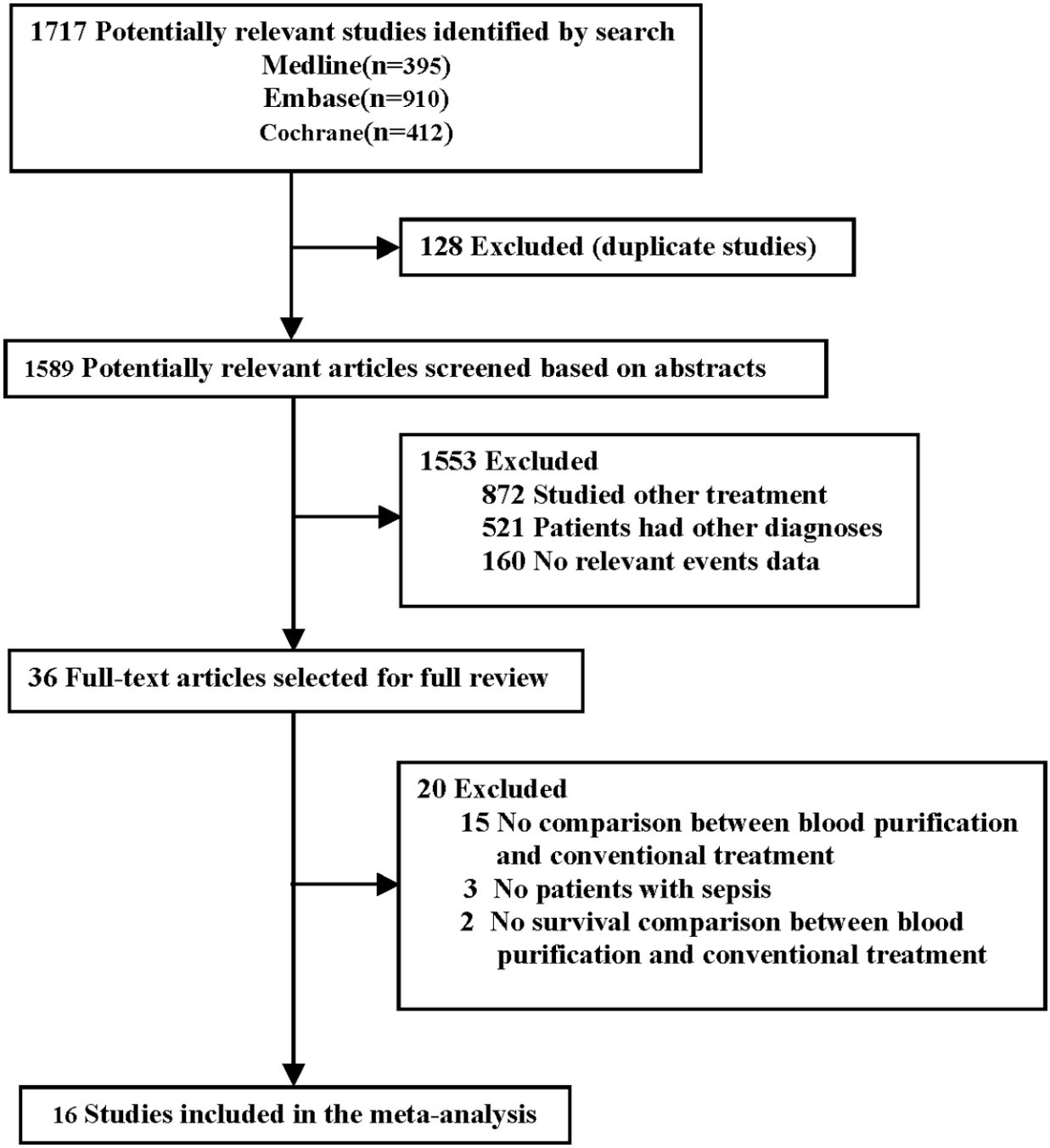


Figure 1.
Quorum Chart of Study Cohort.

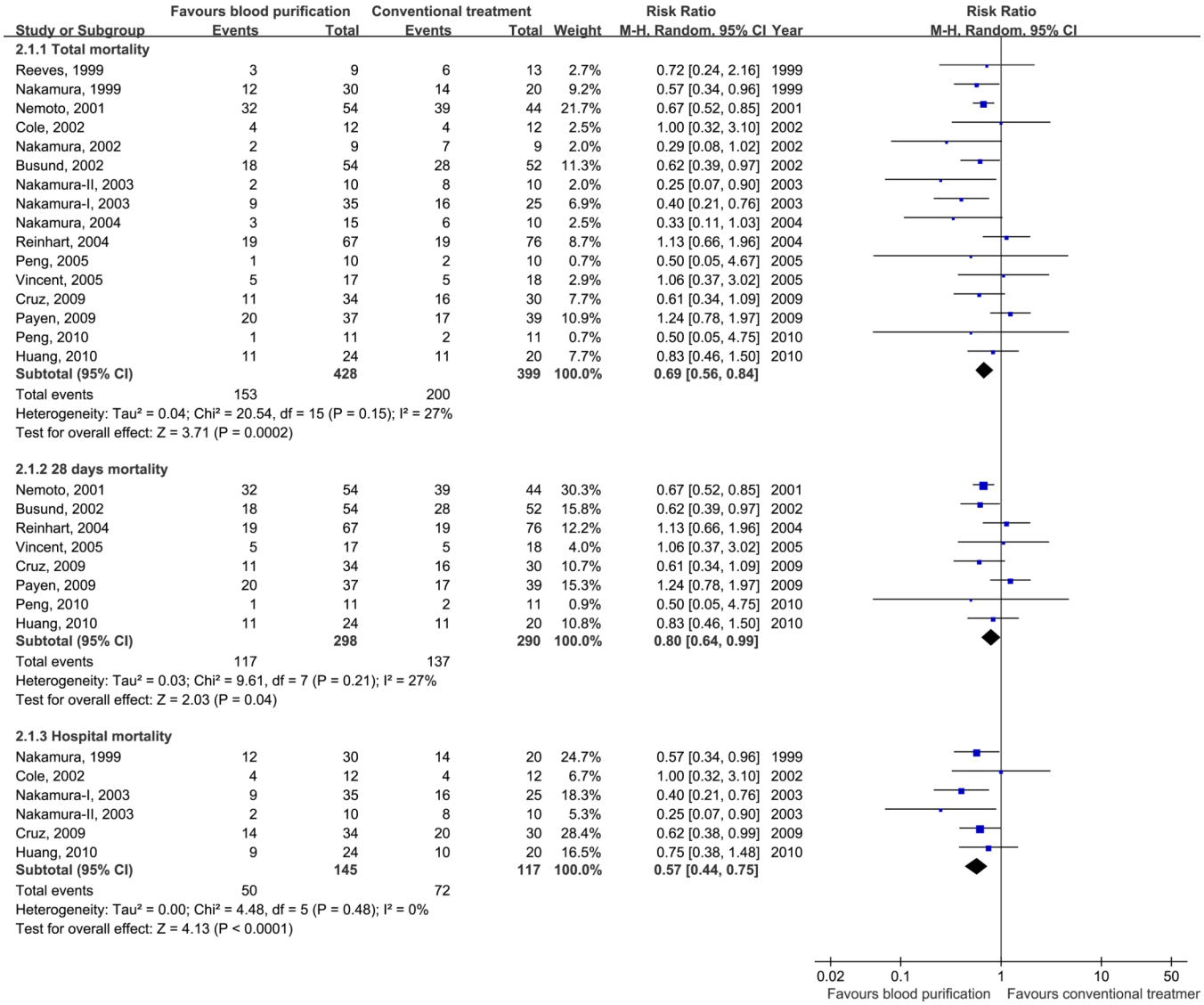
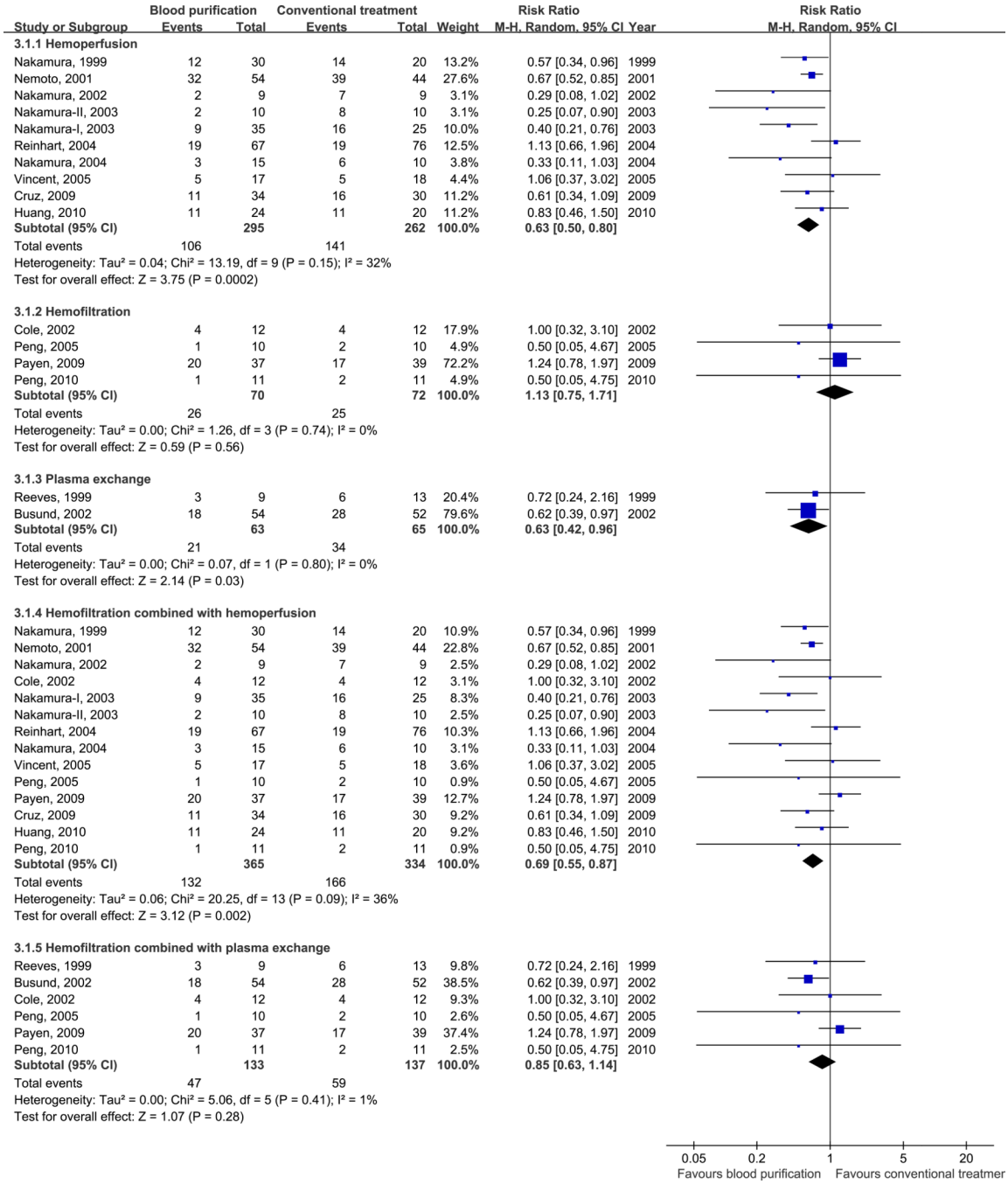


Figure 2.

Risk Ratios (RRs) for Blood Purification versus Conventional Treatment.

Pooled risk ratios are from a random effects model; CI indicates confidence interval; Size of the data markers indicates weight of the study.



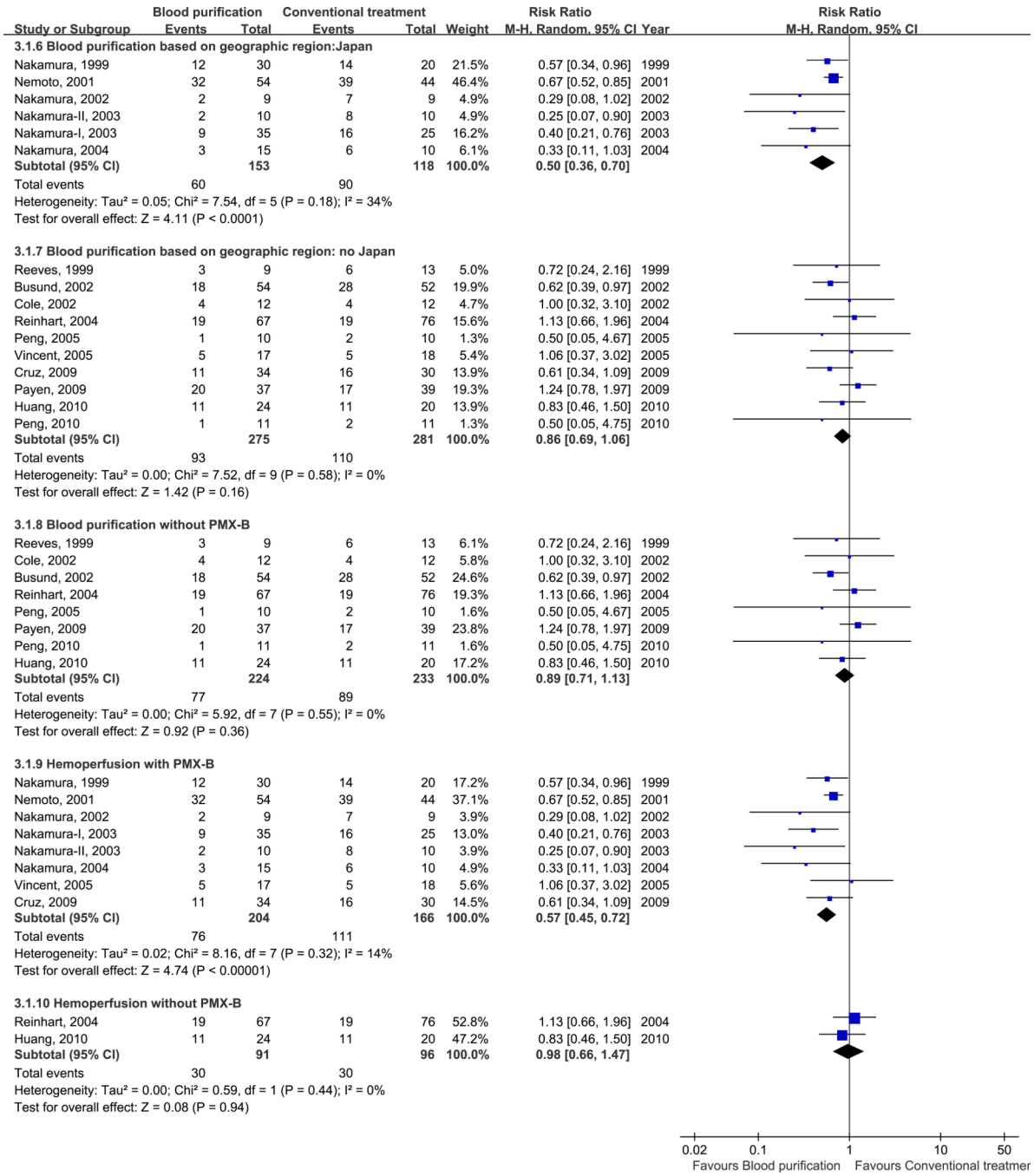


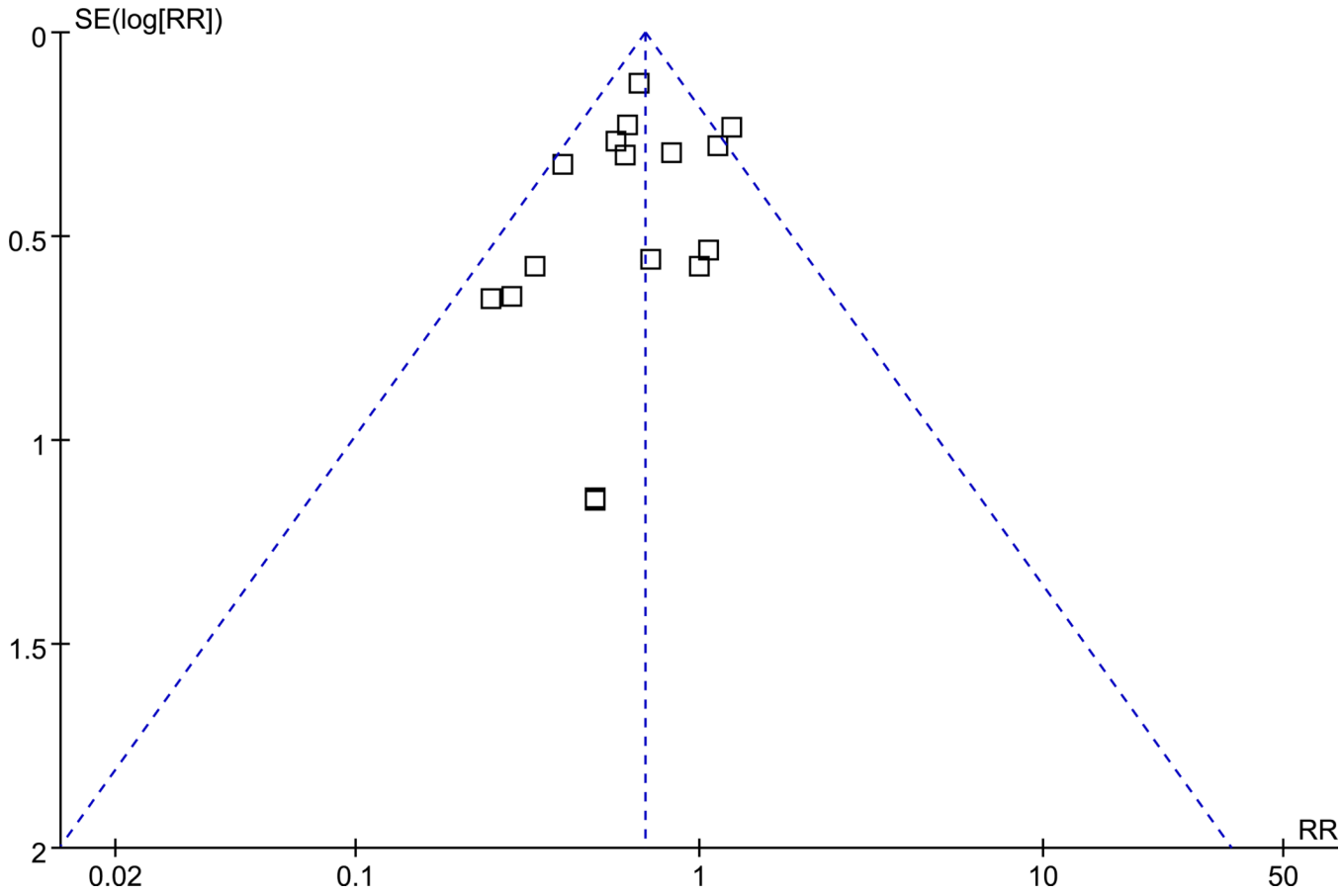
Figure 3.

Risk Ratios (RRs) for Different Modality of Blood Purification versus Conventional Treatment.

Pooled risk ratios are from a random effects model; CI indicates confidence interval; Size of the data markers indicates weight of the study.

A. Different modalities of blood purification versus conventional treatment.

B. Different geographic region and hemoperfusion analysis of blood purification versus conventional treatment.



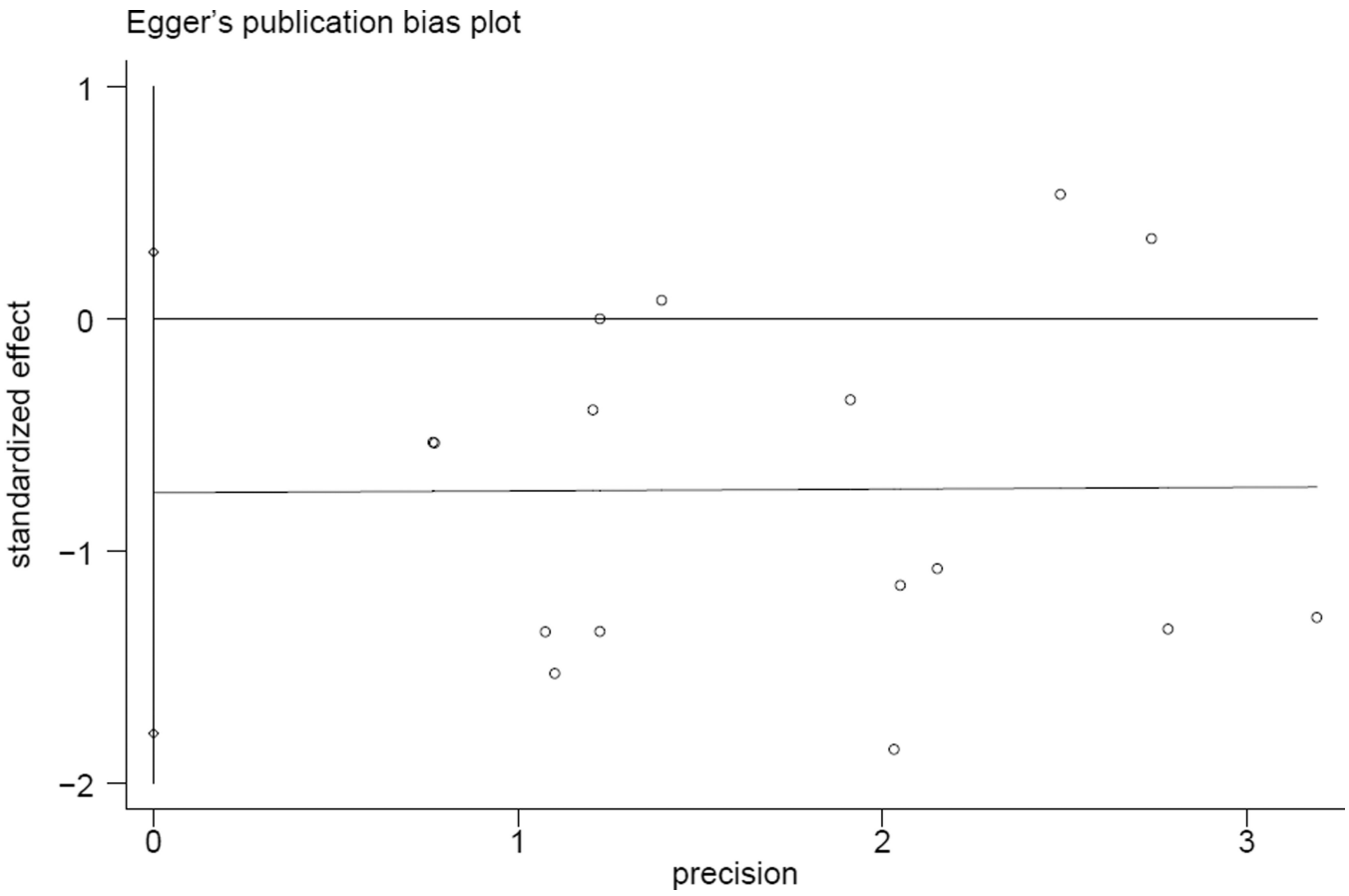


Figure 4.
Assessment of Publication Bias.

A. A funnel plot.

B. Egger's test

Table 1

Baseline characteristics of selected trials of blood purification in sepsis

Source	Country of origin	No. of Patients	Mean Age (years)	Male (%)	Center	Mean APACHE II/III/ SAPS II/ SOFA score	Diagnosis	Jadad Score*
Huang, 2010(23)	China	44	74.9	45.5	S	APACHE II: 28.8 SOFA: 7.6	Severe sepsis or septic shock†	2
Peng, 2010(9)	China	22	53.4	59.1	S	APACHE II:18.6	Severe sepsis†	2
Cruz, 2009(24)	Italy	64	64	65.5	M	APACHE II: 20.5 SOFA: 10	Severe sepsis or septic shock†	5
Payen, 2009(25)	France	76	58.1	74.4	M	SAPS II: 53.4 SOFA:11	Severe sepsis or septic shock†	2
Peng, 2005(26)	China	20	33.2	95	S	N/A	Sepsis†	1
Vincent, 2005(27)	Belgium	35	57.5	63	M	APACHE II: 17.7 SOFA:10.1	Severe sepsis or septic shock†	4
Reinhart, 2004(28)	Germany	143	61.2	62.2	M	APACHE II:28 SOFA:11.8	Severe sepsis or septic shock†	4
Nakamura, 2004(29)	Japan	25	60	75	S	APACHE II:28.2	Severe sepsis†	3
Nakamura, 2003(30)	Japan	20	63.7	60	S	APACHE II:27.3	Sepsis†	2
Nakamura, 2003(31)	Japan	60	55.5	66.7	S	APACHE II:23.5	Sepsis†	4
Busund, 2002(32)	Norway	106	44	56.6	S	APACHE III: 54.9	Severe sepsis or septic shock†	2
Nakamura, 2002(33)	Japan	18	40	66.7	S	APACHE II: 28	Sepsis†	3
Cole, 2002(17)	Australia	24	66.8	58.3	S	APACHE II: 22 SAPS II: 45	Septic shock or septic organ dysfunction†	5
Nemoto, 2001(34)	Japan	98	62	61.2	S	APACHE II: 22.5	Sepsis, severe sepsis or septic shock†	2
Reeves, 1999(35)	Australia	22	59.4	63.6	M	APACHE II: 25.2	Sepsis††	2
Nakamura, 1999(36)	Japan	50	53.8	60	M	APACHE II: 24.8	Septic shock††	1

APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; S, single center trial; M, multicenter trial; N/A, not applicable.

*Jadad score was calculated using investigator-blinding in place of double-blind design.

†Patients were diagnosed according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria;

††Patients were diagnosed according to the other criteria.

Table 2

Blood purification modality and outcome in selected trials

Source	Blood purification			Outcome measures			
	Modality	Intensity	Hemofilter	Mediators cleared	Improved hemodynamics	Improved APACHE II /SAPS II /SOFA score	Improved survival
Huang, 2010(23)	HP	2h per treatment (blood flow rate, 100–200ml/min)	HA330 resin cartridge	IL-6,8	Yes:CI, MAP, SVRI	Yes:SOFA	No:Hospital/28-d survival Yes:ICU survival
Peng, 2010(9)	PHVHF	85ml/kg/h for 6h followed by 35ml/kg/h for 18h, at least 72h	AN69 filter	TNF, IL-1,4,6,10	Yes:SBP, DBP, MAP	Yes:APACHE II/SAPS II /SOFA	No:28-d survival
Cruz, 2009(24)	HP	2h first, and then the second HP for 24h	PMX-B	N/A	Yes:MAP	Yes:SOFA	Yes:Hospital/28-d survival
Payen, 2009(25)	CVVH	2000ml/h for at least 96h	HPM	No:IL-6,IL-1α	N/A	Yes:SOFA	No:28-d survival
Peng, 2005(26)	CVVHDF	1500 –1900 ml /h	AN69 filter	IL-1β,6,8, TNF	N/A	N/A	No: No detail survival days reported
Vincent, 2005(27)	HP	2h per time (blood flow rate,100–200ml/min)	PMX-B	No:Endotoxin,IL-6	Yes:CI, LVSW	No:APACHE II /SOFA	No:28-d survival
Reinhart, 2004(28)	HP	First 4days	Endotoxin adsorber	No:IL-6, TNF-α	N/A	No:APACHE II	No:28-d survival
Nakamura, 2004(29)	HP	Twice within a 24h interval, for 2h at a flow rate of 80 to 100 ml/min	PMX-B	Endotoxin	N/A	N/A	Yes:No detail survival days reported
Nakamura, 2003(30)	HP	Twice within a 24h interval, for 2h at a flow rate of 80 to 100 ml/min	PMX-B	Endotoxin	N/A	N/A	Yes:Hospital survival
Nakamura, 2003(31)	HP	Twice within a 24h interval, for 2h at a flow rate of 80 to 100 ml/min	PMX-B	Endotoxin	N/A	N/A	N/A:Hospital survival
Busund, 2002(32)	Plasma-pheresis	Two treatments: 1820±402 ml first and then 1763±312ml	PF-0.5	N/A	N/A	Yes:APACHE III	No:28-d survival
Nakamura, 2002(33)	HP	Twice within a 24h interval, a flow rate of 100 ml/min	PMX-B	Endotoxin	N/A	No:APACHE II	Yes:No detail survival days reported

Source	Blood purification				Outcome measures		
	Modality	Intensity	Hemofilter	Mediators cleared	Improved hemodynamics	Improved APACHE II /SAPS II /SOFA score	Improved survival
Cole, 2002(17)	CVVH	2 L/h for 48h	AN69 filter	No:TNF-α, IL-6, IL-8, IL-10	N/A	N/A	No:Hospital survival
Nemoto, 2001(34)	HP	4h at a flow rate of 80–100ml/min for once or twice	PMX-B	Endotoxin	Yes:MAP	N/A	Yes:28-d survival
Reeves, 1999(35)	Plasma-filtration	Twice during the first 4–6h and then a lower rate of exchange for another 28–30h	PF1000	No:IL-6	N/A	N/A	No:14-d survival
Nakamura, 1999(36)	HP	Twice within a 24h interval, for 2h at a flow rate of 80–100 ml/min	PMX-B	Endotoxin	Yes:SBP	Yes:APACHE II	Yes:Hospital survival

APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; HP, hemoperfusion; PHVHF, pulse high-volume hemofiltration; HVHF, high volume hemofiltration; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CI, cardiac index; LVHF, low volume hemofiltration; LVSW, left ventricular stroke work index; IL, interleukin; PMX-B, polymyxin B immobilized fiber ; HPM, Heparin-coated polysulfone membrane; PF, plasma filter; N/A, not applicable.

Table 3

Sensitivity analyses of association between blood purification on mortality

	No. of Studies	No. of Patients (Death/Total)		RR (95% CI)	Heterogeneity I^2(*p* value)	Test for effect (*p* value[†])	*p* value for interaction between subgroups[†]
		Blood purification	Conventional treatment				
APACHE II score, mean		Total	Conventional treatment				
≥28	4	35/115	43/115	0.67(0.38–1.21)	53% (.09)	.19	.81
< 28	9	79/212	110/183	0.62(0.52–0.75)	0% (.63)	< .001	
		Hemoperfusion only	Conventional treatment				
≥28	4	35/115	43/115	0.67(0.38–1.21)	53% (.09)	.19	.73
< 28	6	71/180	98/147	0.60(0.49–0.75)	8% (.36)	< .001	
The severity of sepsis [††]		Total	Conventional treatment				
Sepsis	5	17/73	39/67	0.40(0.26–0.64)	0% (.74)	< .001	.01
Severe sepsis or septic shock	10	104/301	122/288	0.79(0.62–1.00)	22% (.24)	.05	
		Hemoperfusion only	Conventional treatment				
Sepsis	3	7/54	31/44	0.20(0.10–0.41)	0% (.63)	< .001	.001
Severe sepsis or septic shock	6	61/187	71/174	0.74(0.54–0.99)	21% (.28)	.05	
Publication year		Total	Conventional treatment				
< 2005	10	104/295	147/271	0.62(0.49–0.78)	26% (.20)	< .001	.04
≥ 2005	6	49/133	53/128	0.90(0.67–1.21)	0% (.51)	.50	
		Hemoperfusion only	Conventional treatment				
< 2005	7	79/220	109/194	0.57(0.40–0.79)	48% (.07)	.0009	.28
≥ 2005	3	27/75	32/68	0.75(0.51–1.11)	0% (.60)	.15	
Age, mean, yrs		Total	Conventional treatment				
≥ 60	7	82/216	103/202	0.70(0.54–0.92)	27% (.22)	.01	.76
< 60	9	71/212	97/197	0.66(0.48–0.91)	35% (.14)	.01	
Jadad score, mean		Total	Conventional treatment				
≥3	7	53/189	73/180	0.64(0.42–0.96)	43% (.10)	.03	.64
<3	9	100/239	127/219	0.71(0.57–0.88)	19% (.28)	.0002	

CI, confidence interval; RR, risk ratio;

† Based on the X^2 test;

†† Based on the report of the studies included.