Review Article

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

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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 to 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, and CIs were calculated using random-effects modeling. Study quality was assessed using Jadad score, and publication bias was assessed using funnel plots and Egger's statistic.

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

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. (*Crit Care Med* 2013; 41:2209–2220)

Key Words: blood purification; cytokines; inflammation; meta-analysis; mortality; sepsis

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 Food and Drug Administration 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 leading to death (5, 6). Because there are correlations between high concentrations of circulating inflammatory cytokines for patients with sepsis or septic shock (7–9) and because 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

*See also p. 2244.

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exchange, and hybrid systems such as 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 with 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 terms and text words with Boolean strategy, and cross-searching of the following three categories: 1) modality of blood purification ("hemofiltration," "renal replacement therapy," "blood purification," "dialysis," "hemoperfusion," "hemoadsorption," "plasmafiltration," or "plasma exchange"); 2) disease ("sepsis," "infection," "septic shock," "systemic inflammatory response syndrome," "SIRS," "multiple organ dysfunction syndrome," or "MODS"); and 3) others related ("outcome," "intensive care unit," "ICU," "critically ill patients," "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 of age more than 18 years . 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 venovenous hemofiltration, regardless of filtration rate, duration, and frequency, were classified as "hemofiltration." Trials of a blood purification technique in which 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 ICU) 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 randomized controlled trial quality is high when scores are greater than or equal to 3. The Jadad/Oxford quality scales require a double-blinded placebo for two of the five 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 were performed independently by two reviewers (F.Z.,Z.P.) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (19), and any discrepancies between the two 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 with the fixed model, we present the results of all analyses according to a random effects model using the method of DerSimonian and Laird that considers both within-study and between-study variations (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 $\geq$ 60 years versus age $<$ 60 years; APACHE score $\geq$ 28 versus $<$ 28; sepsis, severe sepsis versus septic shock; publication year $\geq$ 2005 versus $<$ 2005; Jadad score $\geq$ 3 versus $<$ 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 values less than 0.05 were considered statistically significant. All other statistical analyses were performed using Review Manager, version 5.1.2 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Selection and Characteristics of Trials

Our initial search yielded 1,717 studies (**Fig. 1**). After excluding 128 studies due to duplicate publication, we considered the abstracts of 1,589 studies. After evaluating the abstract of each

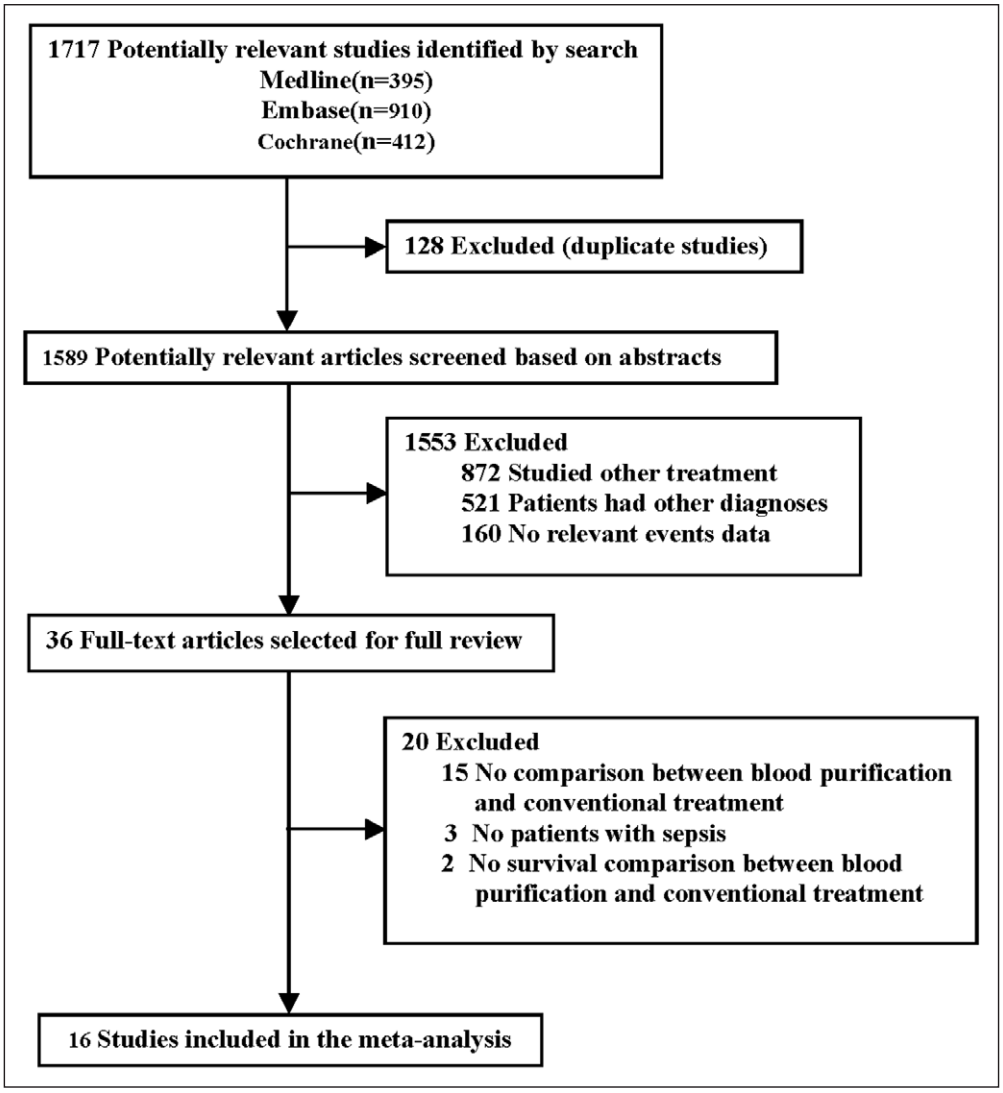

Figure 1. Quorum chart of study cohort.

study, 1,553 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, 23–30) and six multicenter studies (31–36) were identified. These trials were reported between 1999 and 2010. The country of origin in six studies is Japan (25–27, 29, 30, 36), all of which reported on hemoperfusion (Tables 1 and 2). The mean age of the study participants ranged from 33 to 75 years; 637 (77%) patients were admitted to the ICU (17, 24, 25, 27–29, 31–35); and the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 24.2 (9, 17, 23, 25–31, 33–36). 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, whereas 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 (four trials), and plasma exchange (two trials; Table 2). Six trials included in our analysis reported the results of 28-day mortality, and four 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/ Simplified Acute Physiology Score II /Sequential Organ Failure Assessment 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 with 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]; $p = 0.03$; two 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]; $p = 0.56$; four trials, $n = 142$; heterogeneity, $p = 0.74$; **Fig. 3*A***). We also found that hemoperfusion with polymyxin B (PMX-B)

TABLE 1. Baseline Characteristics of Selected Trials of Blood Purification in Sepsis

Source	Country of Origin	No. of Patients	Mean Age (yr)	Male (%)	Center	Mean APACHE II/III/ SAPS II/ SOFA Score	Diagnosis	Jadad Score[a]
Huang et al (23)	China	44	74.9	45.5	S	APACHE II: 28.8; SOFA: 7.6	Severe sepsis or septic shock[b]	2
Peng et al(9)	China	22	53.4	59.1	S	APACHE II:18.6	Severe sepsis[b]	2
Cruz et al(31)	Italy	64	64	65.5	M	APACHE II: 20.5; SOFA: 10	Severe sepsis or septic shock[b]	5
Payen et al(32)	France	76	58.1	74.4	M	SAPS II: 53.4; SOFA:11	Severe sepsis or septic shock[b]	2
Peng et al(24)	China	20	33.2	95	S	N/A	Sepsis[b]	1
Vincent et al(33)	Belgium	35	57.5	63	M	APACHE II: 17.7; SOFA:10.1	Severe sepsis or septic shock[b]	4
Reinhart et al(34)	Germany	143	61.2	62.2	M	APACHE II:28; SOFA:11.8	Severe sepsis or septic shock[b]	4
Nakamura et al(25)	Japan	25	60	75	S	APACHE II:28.2	Severe sepsis[b]	3
Nakamura et al(26)	Japan	20	63.7	60	S	APACHE II:27.3	Sepsis[b]	2
Nakamura et al(27)	Japan	60	55.5	66.7	S	APACHE II:23.5	Sepsis[b]	4
Busund et al(28)	Norway	106	44	56.6	S	APACHE III: 54.9	Severe sepsis or septic shock[b]	2
Nakamura et al(29)	Japan	18	40	66.7	S	APACHE II: 28	Sepsis[b]	3
Cole et al(17)	Australia	24	66.8	58.3	S	APACHE II: 22; SAPS II: 45	Septic shock or septic organ dysfunction[b]	5
Nemoto et al(30)	Japan	98	62	61.2	S	APACHE II: 22.5	Sepsis, severe sepsis or septic shock[b]	2
Reeves et al(35)	Australia	22	59.4	63.6	M	APACHE II: 25.2	Sepsis[c]	2
Nakamura et al(36)	Japan	50	53.8	60	M	APACHE II: 24.8	Septic shock[c]	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, NA = not applicable.

[a]Jadad score was calculated using investigator blinding in place of double-blind design.

[b]Patients were diagnosed according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria.

[c]Patients were diagnosed according to the other criteria.

decreased mortality in patients with sepsis (RR, 0.57 [95% CI, 0.45–0.72]; $p < 0.001$; eight trials, $n = 370$; heterogeneity, $p = 0.32$), whereas hemoperfusion without PMX-B (RR, 0.98 [95% CI, 0.66–1.47]; $p = 0.94$; two 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]; $p = 0.36$; eight trials, $n = 457$; heterogeneity, $p = 0.55$) did not (**Fig. 3*B***). 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]; $p = 0.28$; six 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]; $p < 0.001$; six trials; $n = 271$; heterogeneity, $p = 0.18$), whereas pooled 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. 3*B*).

TABLE 2. Blood Purification Modality and Outcome in Selected Trials

	Blood Purification				Outcome Measures		
Source	Modality	Intensity	Hemofilter	Mediators Cleared	Improved Hemodynamics	Improved APACHE II/SAPS II/SOFA Score	Improved Survival
Huang et al (23)	HP	2 hr per treatment (blood flow rate, 100–200 mL/min)	HA330 resin cartridge	IL-6, IL-8	Yes: CI, MAP, SVRI	Yes: SOFA	No: Hospital/28-d survival; Yes: ICU survival
Peng et al (9)	PHVHF	85 mL/kg/hr for 6 hr followed by 35 mL/kg/hr for 18 hr, at least 72 hr	AN69 filter	TNF, IL-1,4,6,10	Yes: SBP, DBP, MAP	Yes: APACHE II/SAPS II/SOFA	No: 28-d survival
Cruz et al (31)	HP	2 hr first, and then the second HP for 24 hr	PMX-B	NA	Yes: MAP	Yes: SOFA	Yes: Hospital/28-d survival
Payen et al (32)	CVVH	2000 mL/hr for at least 96 hr	HPM	No: IL-6, IL-1α	NA	Yes: SOFA	No: 28-d survival
Peng et al (24)	CVVHDF	1500–1900 mL/hr	AN69 filter	IL-1β,6,8, TNF	NA	NA	No: No detail survival days reported
Vincent et al (33)	HP	2 hr per time (blood flow rate,100–200 mL/min)	PMX-B	No: Endotoxin, IL-6	Yes: CI, LVSW	No: APACHE II/SOFA	No: 28-d survival
Reinhart et al (34)	HP	First 4 d	Endotoxin adsorber	No: IL-6, TNF-α	NA	No: APACHE II	No: 28-d survival
Nakamura et al (25)	HP	Twice within a 24 hr interval, for 2 hr at a flow rate of 80–100 mL/min	PMX-B	Endotoxin	NA	NA	Yes: No detail survival days reported
Nakamura et al (26)	HP	Twice within a 24-hr interval, for 2 hr at a flow rate of 80–100 mL/min	PMX-B	Endotoxin	NA	NA	Yes: Hospital survival
Nakamura et al (27)	HP	Twice within a 24 hr interval, for 2 hr at a flow rate of 80–100 mL/min	PMX-B	Endotoxin	NA	NA	NA: Hospital survival
Busund et al (28)	Plasma pheresis	Two treatments: 1820 ± 402 mL first and then 1763 ± 312 mL	PF-0.5	NA	NA	Yes: APACHE III	No: 28-d survival
Nakamura et al (29)	HP	Twice within a 24-hr interval, a flow rate of 100 mL/min	PMX-B	Endotoxin	NA	No: APACHE II	Yes: No detail survival days reported
Cole et al (17)	CVVH	2 L/hr for 48 hr	AN69 filter	No: TNF-α, IL-6, IL-8, IL-10	NA	NA	No: Hospital survival
Nemoto et al (30)	HP	4 hr at a flow rate of 80–100 mL/min for once or twice	PMX-B	Endotoxin	Yes: MAP	NA	Yes: 28-d survival

(*Continued*)

TABLE 2. *(Continued).* 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
Reeves et al (35)	Plasma filtration	Twice during the first 4–6 hr and then a lower rate of exchange for another 28–30 hr	PF1000	No: IL-6	NA	NA	No: 14-d survival
Nakamura et al (36)	HP	Twice within a 24-hr interval, for 2 hr 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, IL = interleukin, CI = cardiac index, MAP = mean arterial pressure, PHVHF = pulse high-volume hemofiltration, TNF = tumor necrosis factor, SBP = systolic blood pressure, DBP = diastolic blood pressure, PMX-B = polymyxin B immobilized fiber, CVVH = continuous venovenous hemofiltration, HPM = Heparin-coated polysulfone membrane, CVVHDF = continuous venovenous hemodiafiltration, LVSW = left ventricular stroke work index, PF = plasma filter, NA = not applicable.

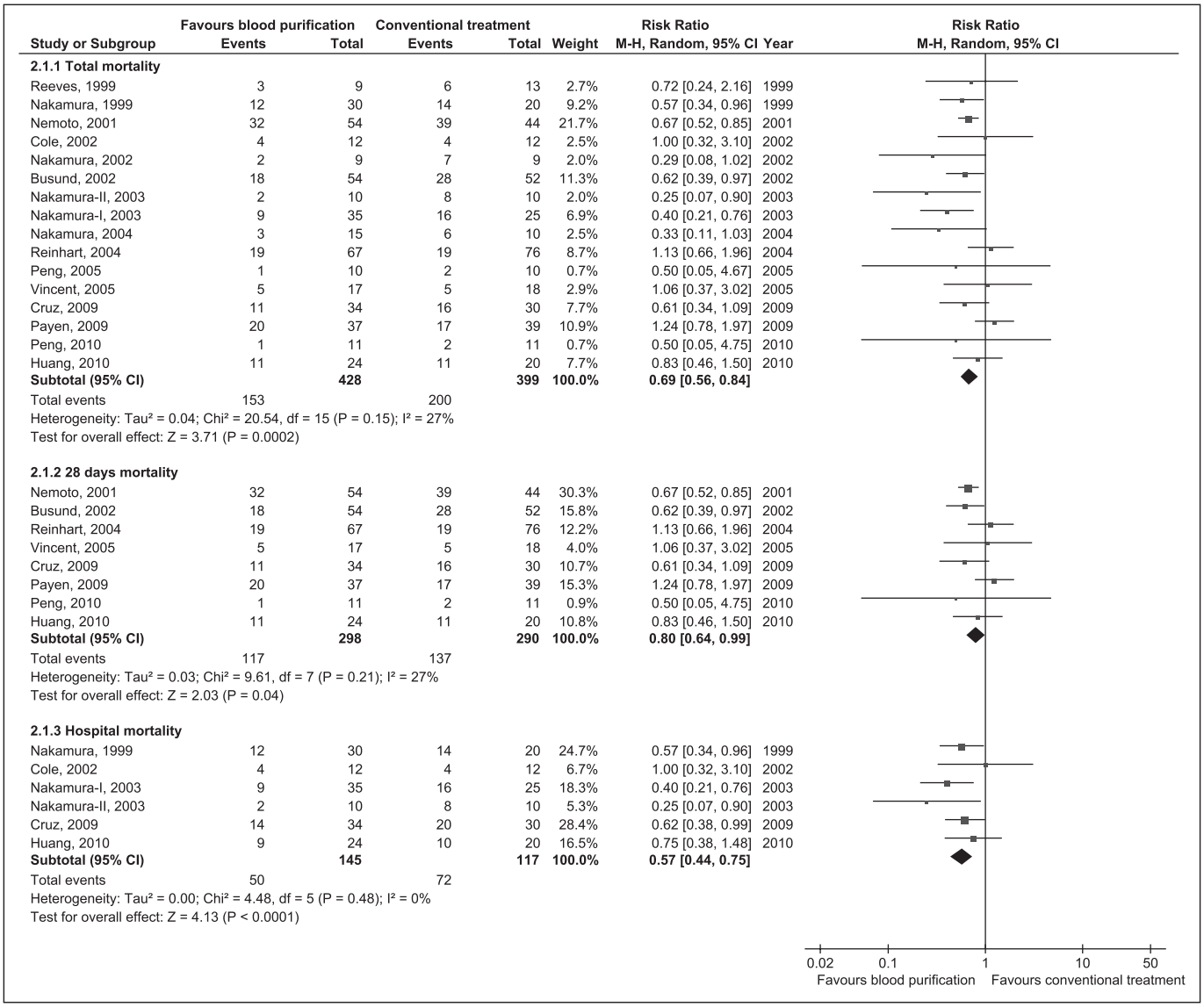

Figure 2. Risk ratios for blood purification versus conventional treatment. Pooled risk ratios are from a random effects model; size of the data markers indicates weight of the study. MH = Mantel-Haenszel.

TABLE 3. Sensitivity Analyses of Association Between Blood Purification on Mortality

	No. of Studies	No. of Patients (Death/Total)		Risk Ratio (95% CI)	Heterogeneity I^2(p)	Test for Effect (p^a)	p for Interaction Between Subgroups[a]
		Blood Purification	Conventional Treatment				
Acute Physiology and Chronic Health Evaluation II score, mean		Total	Conventional treatment				
≥28	4	35/115	43/115	0.67(0.38–1.21)	53% (0.09)	0.19	0.81
<28	9	79/212	110/183	0.62(0.52–0.75)	0% (0.63)	<.001	
		Hemoperfusion only	Conventional treatment				
≥28	4	35/115	43/115	0.67(0.38–1.21)	53% (0.09)	0.19	0.73
<28	6	71/180	98/147	0.60(0.49–0.75)	8% (0.36)	<0.001	
The severity of sepsis [b]		Total	Conventional treatment				
Sepsis	5	17/73	39/67	0.40(0.26–0.64)	0% (0.74)	<0.001	0.01
Severe sepsis or septic shock	10	104/301	122/288	0.79(0.62–1.00)	22% (0.24)	0.05	
		Hemoperfusion only	Conventional treatment				
Sepsis	3	7/54	31/44	0.20(0.10–0.41)	0% (0.63)	<0.001	0.001
Severe sepsis or septic shock	6	61/187	71/174	0.74(0.54–0.99)	21% (0.28)	0.05	
Publication year		Total	Conventional treatment				
<2005	10	104/295	147/271	0.62(0.49–0.78)	26% (0.20)	<0.001	0.04
≥2005	6	49/133	53/128	0.90(0.67–1.21)	0% (0.51)	0.50	
		Hemoperfusion only	Conventional treatment				
<2005	7	79/220	109/194	0.57(0.40–0.79)	48% (0.07)	0.0009	0.28
≥2005	3	27/75	32/68	0.75(0.51–1.11)	0% (0.60)	0.15	
Age, mean, yr		Total	Conventional treatment				
≥60	7	82/216	103/202	0.70(0.54–0.92)	27% (0.22)	0.01	0.76
<60	9	71/212	97/197	0.66(0.48–0.91)	35% (0.14)	0.01	
Jadad score, mean		Total	Conventional treatment				
≥3	7	53/189	73/180	0.64(0.42–0.96)	43% (0.10)	0.03	0.64
<3	9	100/239	127/219	0.71(0.57–0.88)	19% (0.28)	0.0002	

[a]Based on the χ^2 test.

[b]Based on the report of the studies included.

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 vs <60 yr) and mean APACHE II score (≥28 vs <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]; $p < 0.001$; five trials, $n = 140$) compared with

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 vs < 60 yr), mean APACHE II score (≥28 vs <28) at enrollment, or publication year (before 2005 vs 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, 33). Cruz et al (31) reported some adverse reactions, including cartridge clotting (four cases, 6%), hypotension (1 case, 1.5%), and tachycardia (two cases, 3%). Busund et al (28) 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 article 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 greater than or equal to 3, whereas nine 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. 4**, ***A*** and ***B***).

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 venovenous hemofiltration (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 multicentered 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, 32), 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 due to 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 continuous venovenous hemofiltration 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 PMX-B fiber column appears to improve survival compared with conventional treatment (25, 26, 29–31, 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, although 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, nonsevere sepsis). This finding may be of particular importance because many sepsis trials have focused on patients with severe disease (9, 17, 23, 25, 28, 31–34, 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 younger than 60 years old compared with older patients. In a cohort study, Brar et al (45) 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%).

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

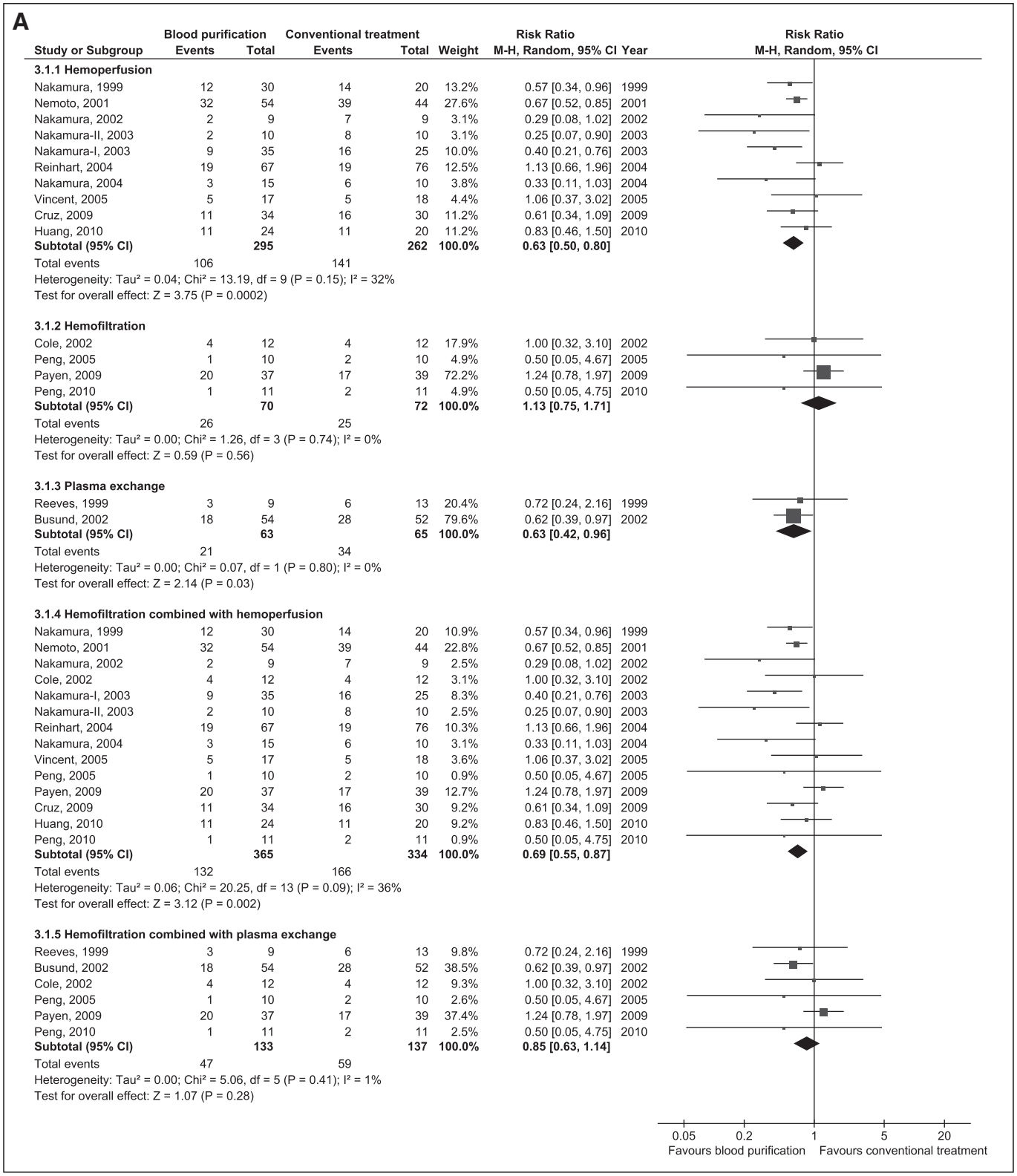

Figure 3. Risk ratios for different modality of blood purification versus conventional treatment. Pooled risk ratios are from a random effects model; size of the data markers indicates weight of the study. **A**, Different modalities of blood purification versus conventional treatment. **B**, Different geographic region and hemoperfusion analysis of blood purification versus conventional treatment. M-H = Mantel-Haenszel.

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

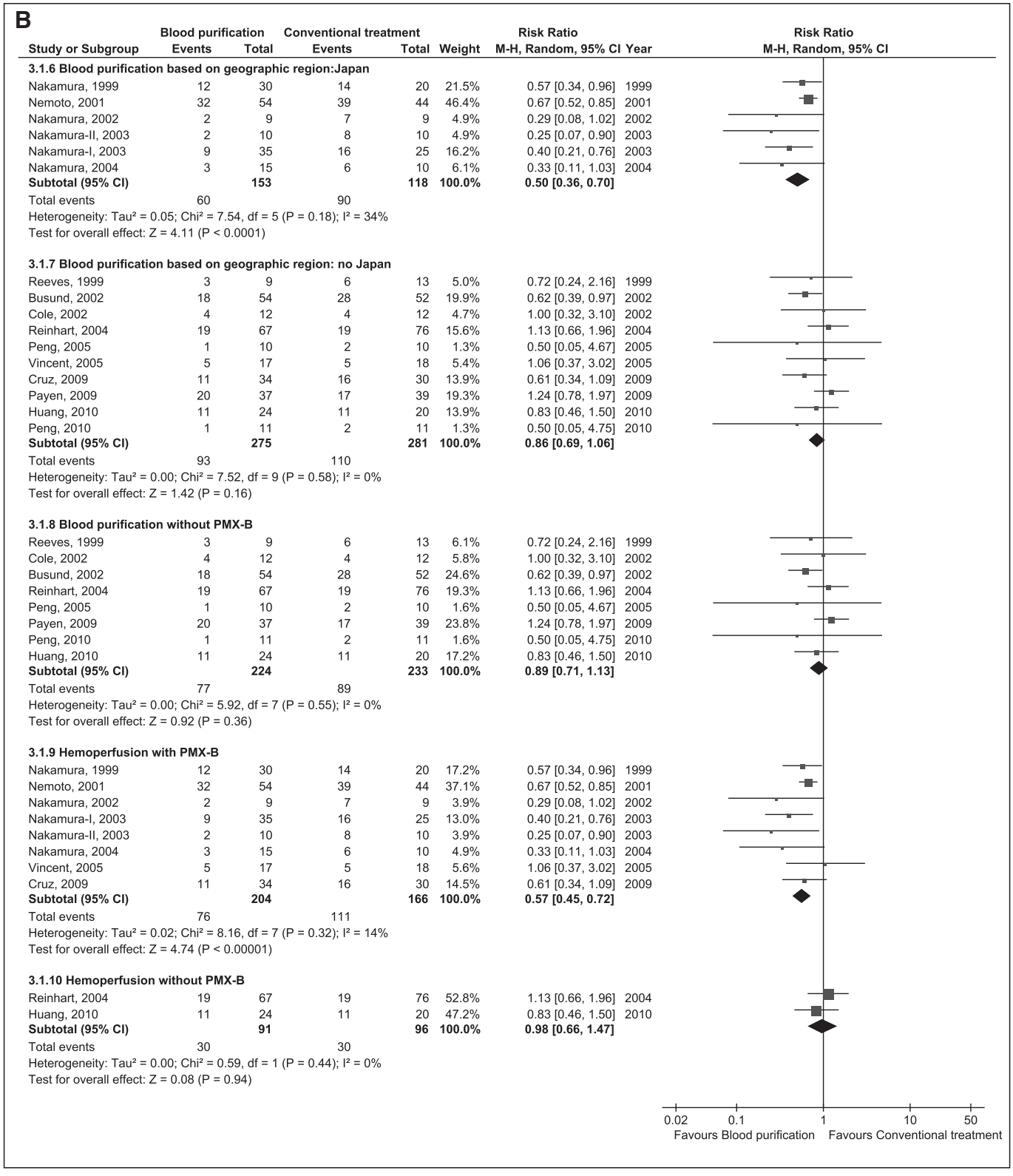

Figure 3. (Continued)

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

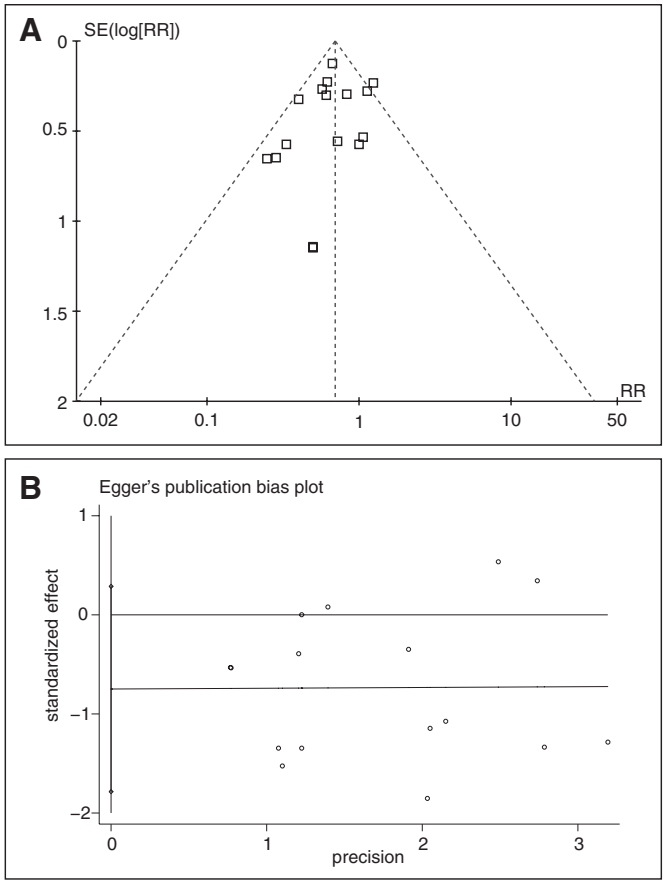

Figure 4. Assessment of publication bias. **A**, A funnel plot. **B**, Egger's test. SE = standard error, RR = risk ratio.

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 because 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 with peak concentration-dependent kinetics (50). Because 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 (25–27, 29, 30, 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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