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Effect of high-volume hemofiltration on mortality in critically ill patients
A PRISMA-compliant systematic review and meta-analysis

Yusheng Luo, BS[a],[*], Guijun Sun, BS[a], Cailian Zheng, BS[a], Mei Wang, BS[a], Juan Li, BS[a], Jie Liu, BS[a], Yuqiang Chen, BS[b], Wei Zhang, BS[c], Yanling Li, BS[d]

Abstract

Background: High-volume hemofiltration (HVHF) is widely used for blood purification in critically ill patients with systemic inflammatory syndromes. The purpose of this study was to evaluate the effect of HVHF on mortality at different follow-up periods in critically ill patients.

Methods: We systematically searched PubMed, Embase, and the Cochrane Library through April 2017 to identify trials that evaluated the effect of HVHF on mortality in critically ill patients. Summary relative risks (RRs) and 95% confidence intervals (CIs) were employed to calculate the treatment effect using a random effects model. Eleven trials involving 1048 critically ill patients were included in this study.

Results: The summary results indicated no significant differences between HVHF and usual care for the incidence of 28-day mortality (RR: 0.93; 95%CI: 0.80–1.08; $P = .321$), 7-day mortality (RR: 0.72; 95%CI: 0.50–1.03; $P = .072$), 60-day mortality (RR: 1.00; 95%CI: 0.86–1.16; $P = .997$), and 90-day mortality (RR: 1.01; 95%CI: 0.88–1.16; $P = .927$). Subgroup analysis suggested HVHF significantly reduced the risk of 28-day mortality (RR: 0.64; 95%CI: 0.42–0.97; $P = .035$) if pooled the study sample size < 100.

Conclusion: Our findings suggest HVHF significantly reduced the incidence of 28-day mortality when pooled the study sample size < 100. Further, HVHF had a marginal effect on the incidence of 7-day mortality.

Abbreviations: ARDS = acute respiratory distress syndrome, CIs = confidence intervals, HVHF = high-volume hemofiltration, RCTs = randomized controlled trials, RRs = relative risks.

Keywords: critically ill patients, HVHF, meta-analysis, RCT

1. Introduction

Critical illness is characterized by inflammatory injury, cellular immune dysfunction, oxidative stress, and mitochondrial dysfunction,[1–3] which causes approximately 40% to 50% mortality among patients with acute respiratory distress syndrome (ARDS), and up to 45% mortality for patients with other critical diseases.[4,5] The most common manifestations in ARDS patients include inflammation, parenchymal cell proliferation, and disordered deposition of collagen.[6,7] Although

oxidative stress is not an epiphenomenon in critically ill patients, underlying pathophysiologic events can lead to mitochondrial dysfunction and systemic inflammatory response syndrome.[8]

The goal of treatment in critically ill patients is to prevent systemic inflammation, sequelae, and mortality.[9,10] Journois et al[11] introduced very HVHF as a blood purification technique in humans in 1996. Previous meta-analysis indicated no significant beneficial effect of HVHF or pulse HVHF compared to standard-volume hemofiltration in critically ill patients, but this included a small number of trials and did not illustrate the treatment effects in patients with specific characteristics.[12] Recently, numerous trials evaluated the effect of HVHF on mortality in critically ill patients at different follow-up durations. These trials should be pooled and re-evaluated the treatment effect between HVHF and usual care on mortality. Therefore, we conducted this systematic review and meta-analysis based on available randomized controlled trials (RCTs) to compare HVHF with usual care on the risk of mortality at different follow-up duration periods.

2. Methods

2.1. Data sources and search strategies

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Checklist S1).[13] This study does not require ethical approval and patient consent because the study was a systematic review and meta-analysis of previous studies and does

not involve patients. Three electronic databases, PubMed, Embase, and the Cochrane Library, were searched for studies published since the beginning of HVHF in the treatment of critically ill patients through April 2017. The authors used the keywords (hemofiltration OR haemofiltration OR hemodialysis OR haemodialysis OR hemodiafiltration OR haemodiafiltration) AND ("high volume" OR "high-volume" OR "high dose" OR "high-dose") AND (septic OR sepsis OR critical illness). The study type was restricted to randomized controlled design; the published language or publication status was not restricted. Manual searches of reference lists from all relevant original and review articles were conducted to identify additional eligible trials. Study topic, methods, disease status, study design, intervention, control, and outcomes were employed to identify relevant studies.

The literature retrieval was performed in duplicate by 2 independent reviewers, and any disagreement was settled by discussed with each other referring to original trial. The study was eligible if the following criteria were met: the study had an RCT design; the trial compared HVHF with usual care in treatment of critically ill patients; the primary outcome was 28-day mortality, and the secondary outcomes included 7-day, 60-day, and 90-day mortality. For the trials without adequate data, we contacted the authors to get the unpublished results, and if the author could not provide the necessary data, the trials were excluded.

2.2. Data collection and quality assessment

Data collection was conducted by 2 reviewers independently. Publication information (first author's name, publication year), characteristics of patients (country, sample size, mean age, percentage male, disease status, intervention, control, and follow-up duration), and mortality at different follow-up periods were collected. Any inconsistency was settled by a third reviewer for consensus. Furthermore, 2 reviewers independently evaluated the quality of trials by using the Jadad guidelines.[14] The Jadad scale assesses the reporting of essential points to a RCT (i.e., randomization, blinding, withdrawals, and dropouts). Group discussion was used to resolve disagreements.

2.3. Statistical analysis

The effect of HVHF on mortality in critically ill patients was calculated based on the number of events and sample size in each group in individual trials. The random effects model was employed to calculate pooled relative risks (RRs) and 95% confidence intervals (CIs) for HVHF versus usual care.[15,16] Heterogeneity among included trials was investigated using the Q statistic; a P value <.10 was indicative of significant heterogeneity.[17] The source of heterogeneity was explored for 28-day mortality using univariate meta-regression according to sample size, mean age, and percentage male.[18] Sensitivity analyses were performed by removing each individual trial from the meta-analysis to evaluate the influence of a single study in the meta-analysis.[19] Subgroup analysis was conducted for 28-day mortality based on publication year, country, sample size, mean age, percentage male, control, and study quality. P value for heterogeneity between subgroups was evaluated using Chi-square test. A funnel plot was performed to qualitatively evaluate the publication bias for 28-day mortality. Further, the Egger et al[20] and Begg test[21] results were employed to quantitatively evaluate publication bias. The reported P values for pooled

results were 2-sided, and P values <0.05 were regarded as statistically significant. Statistical analyses were conducted using Stata software (version 10.0; Stata Corporation, College Station, TX).

3. Results

The results of the study selection process are shown in Figure 1. We identified 912 articles from our initial electronic search, of which 869 were excluded after omitting duplicate and irrelevant studies. We retrieved the full text for the remaining 43 potentially eligible trials. After detailed evaluations, 11 RCTs were selected for the final meta-analysis.[22–32] A manual search of the reference lists of these studies did not yield any new eligible studies. The general characteristics of the included studies are presented in Table 1.

Eleven trials involving a total of 1,048 critically ill patients were included in this meta-analysis. The patients' ages ranged from 38.5 to 70.4 years, and each trial contained between 19 and 280 patients. Four trials were conducted in France, 5 in China, one in the Netherlands, and one in Malaysia. Of these trials, 2 trials reported patients with septic shock, 3 reported patients with sepsis, 2 included ARDS patients, one trial included patients with postcardiac surgery shock, one trial included patients with acute renal failure, one trial included patients with acute kidney injury, and one trial included patients with multiple organ dysfunction syndrome (MODS). Study quality was evaluated by using the Jadad scale. Here we regarded a trial with a score ≥ 4 as being high quality. Overall, 2 trials had a score of 4, 4 trials had a score of 3, and the remaining 5 trials had a score of 2.

Data for the effect of HVHF on the incidence of 28-day mortality were available from nine trials, including 907 critical illness patients with 365 mortality events. We noted HVHF therapy reduced the risk of 28-day mortality by 7%, but this was not statistically significant (RR: 0.93; 95%CI: 0.80–1.08; without evidence of heterogeneity ([I-square: 0.0%; P=.767]; Fig. 2). Sensitivity analysis indicated the results were not affected by sequential exclusion of any particular trial (Table 2).

Data for the effect of HVHF on the incidence of 7-day, 60-day, and 90-day mortality were available from 2, 3, and 4 trials, respectively. Overall, we noted HVHF therapy had little or no significant effect on the incidence of 7-day mortality (RR: 0.72; 95%CI: 0.50–1.03; P=.072; without evidence of heterogeneity [I-square: 0.0%; P=.981]; Fig. 3A), 60-day mortality (RR: 1.00; 95%CI: 0.86–1.16; P=.997; without evidence of heterogeneity [I-square: 0.0%; P=.615]; Fig. 3B), and 90-day mortality (RR: 1.01; 95%CI: 0.88–1.16; P=.927; without evidence of heterogeneity [I-square: 0.0%; P=.450]; Fig. 3C).

Meta-regression analysis was conducted for 28-day mortality based on sample size, mean age, and percentage male. We noted that sample size (P=.136), mean age (P=.723), and percentage male (P=.487) were not significant factors contributing to the effect of HVHF therapy on the incidence of 28-day mortality. Further, the findings of subgroup analysis indicated HVHF significantly reduced the incidence of 28-day mortality when the sample size was <100 (RR: 0.64; 95%CI: 0.42–0.97; P=.035). Further, we noted HVHF might play a non-significant preventive effect on the risk of 28-day mortality when compared with conservative therapy (RR: 0.54; 95%CI: 0.29–1.01; P=.053). There were no other significant differences between HVHF and usual care for the incidence of 28-day mortality based on other factors (Table 3).
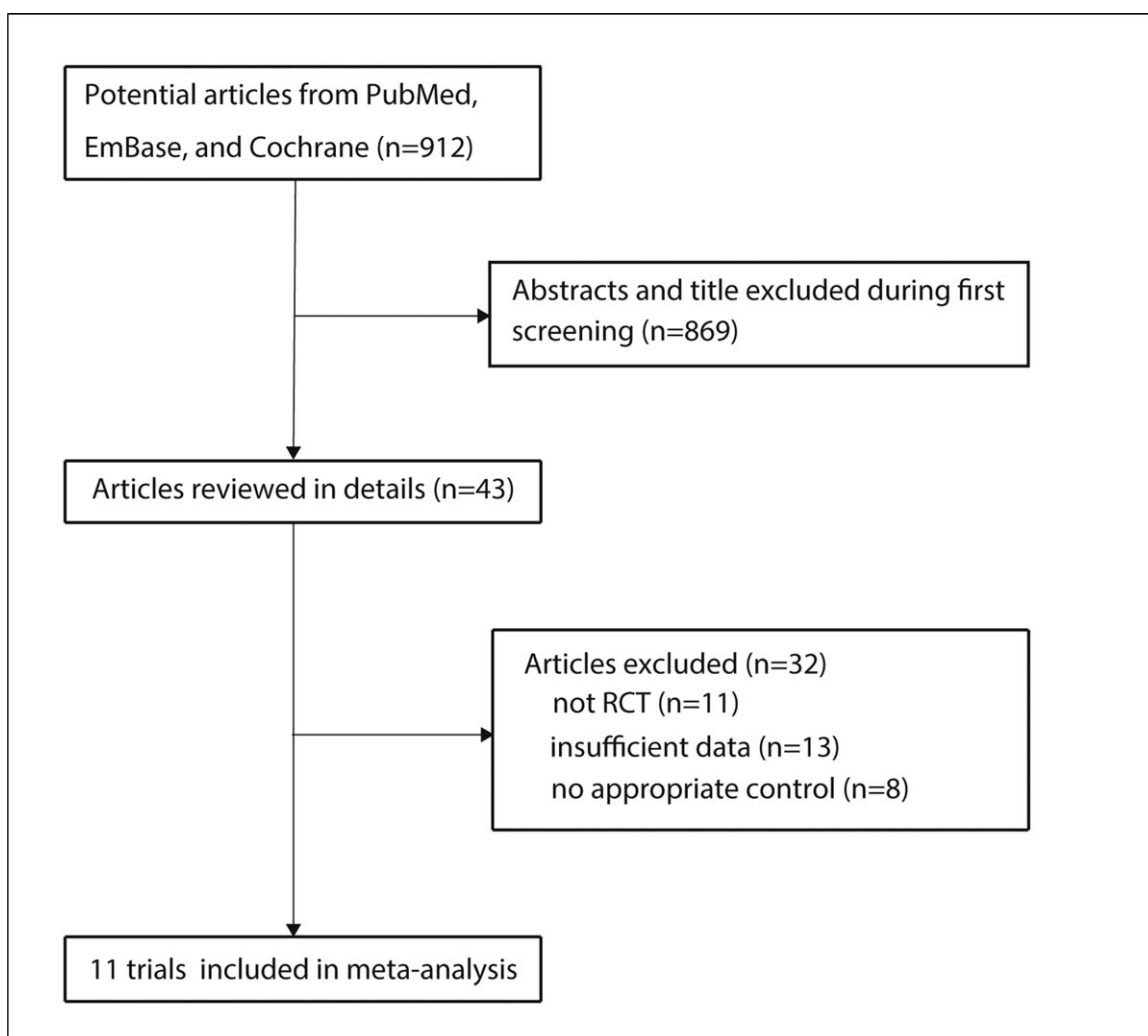
Figure 1. Study selection process.

Table 1

Baseline characteristics of studies included.

Study	Publication years	Country	Sample size	Mean age, years	Percentage male (%)	Disease status	Intervention	Control	Follow-up duration	Jadad score
Quenot et al[22]	2015	France	60	66.6	70.0	Septic shock	HVHF (120 mL/kg/ h)	Usual care (recommendations of the Surviving Sepsis Campaign for severe sepsis)	90 days	2
Combes et al[23]	2015	France	224	59.5	79.5	Postcardiac surgery shock	HVHF (80 mL/kg/h)	Usual care (standard-volume continuous venovenous hemodiafiltration)	90 days	4
Zhang et al[24]	2013	China	65	43.0	40.0	ARDS	HVHF (45 mL/kg/h)	Usual care (mechanical ventilation and medication)	28 days	3
Chen et al[25]	2014	China	105	38.5	63.8	ARDS	HVHF (200–250 mL/min)	Usual care (mechanical ventilation and medication)	7 days	3
Peng et al[26]	2010	China	22	53.4	59.1	Severe sepsis	HVHF (250–300 mL/min)	Usual care (conventional treatment)	28 days	2
Bouman et al[27]	2002	Netherland	70	69.0	58.5	Acute renal failure	HVHF (200 mL/min)	Usual care (early low-volume hemofiltration 100–150 mL/min)	28 days	2
Boussekey et al[28]	2008	France	19	70.4	78.9	Septic shock	HVHF (65 mL/kg/h)	Usual care (low-volume hemofiltration 35 mL/kg/ h)	28 days	2
Joannes-Boyau et al[29]	2013	France	140	69.0	60.6	AKI	HVHF (70 mL/kg/h)	Usual care (standard-volume hemofiltration 35 mL/kg/ h)	90 days	4
Zhang et al[31]	2013	China	30	43.1	50.0	MODS	HVHF (85 mL/kg/h)	Usual care (standard continuous venovenous hemofiltration 35 mL/kg/ h)	28 days	2
Ghani et al[32]	2012	China	280	58.3	61.4	Sepsis and AKI	HVHF (85 mL/kg/h)	Usual care (standard continuous venovenous hemofiltration 50 mL/kg/ h)	90 days	3
Duval et al[33]	2006	Malaysia	33	57.7	57.6	Sepsis	HVHF (100 mL/kg/ h)	Usual care (continuous venovenous haemofiltration 35 mL/kg/ h)	50 days	3

AKI = acute kidney injury, HVHF = high-volume hemofiltration, MODS = multiple organ dysfunction syndrome, MV = mechanical ventilation, RRT = renal replacement therapy, SOFA = sequential organ failure assessment.
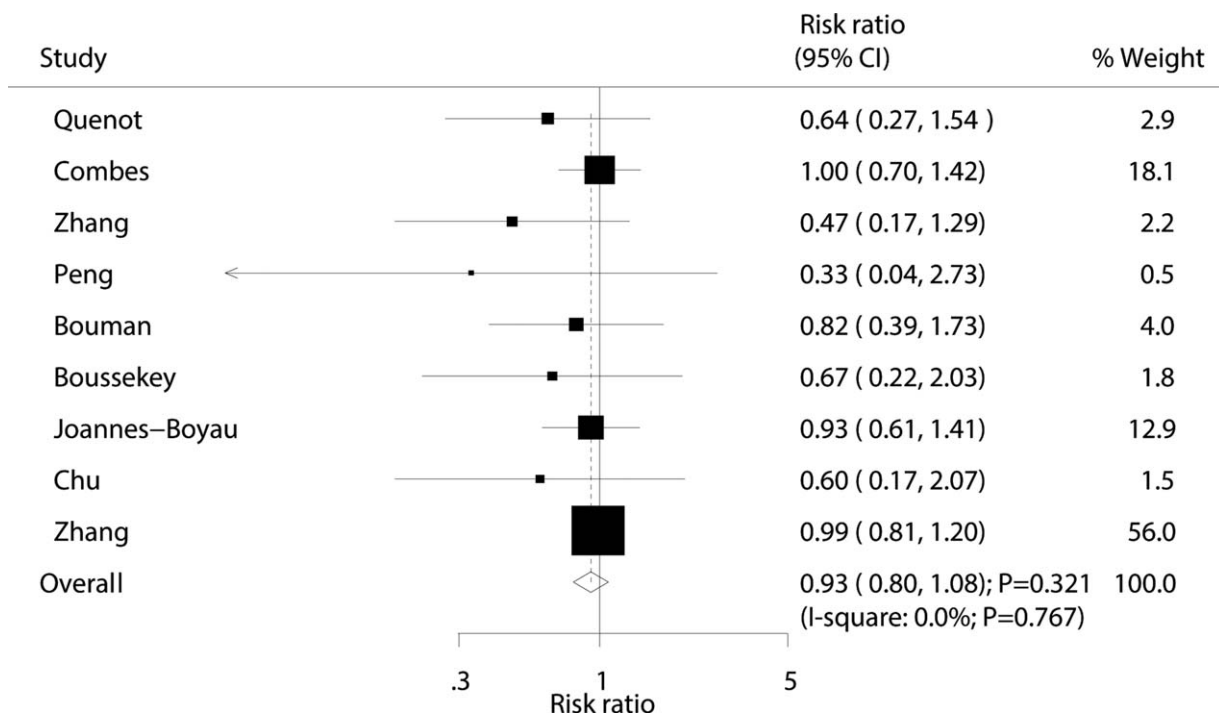
Figure 2. Effect of HVHF on the incidence of 28-days mortality. HVHF=high-volume hemofiltration.

Review of the funnel plot could not rule out the potential for publication bias for 28-day mortality. Further, the Egger and Begg test results showed significant publication bias for 28-day mortality (P value for Egger: <.001; P value for Begg: .009) (Fig. 4). The conclusions were not changed after adjustment for publication bias by using the trim and fill method.[33]

4. Discussion

The purpose of this meta-analysis was to determine the effect of HVHF on mortality in critically ill patients. Eleven RCTs were identified and included 1,048 patients with various baseline characteristics. The findings of this study suggest that HVHF was not associated with the incidence of 7-day, 28-day, 60-day, and 90-day mortality. Subgroup analysis revealed that HVHF significantly reduced the risk of 28-day mortality when the sample size was <100. These results could help to better define the treatment effect of HVHF on mortality at different follow-up periods in critically ill

patients, and could help physicians select the appropriate approach in treating critical illnesses.

A previous meta-analysis suggested that HVHF did not affect the incidence of mortality at different follow-up periods in critically ill patients. However, this study encountered criticism because it was based on limited trials and had insufficient information to provide strong evidence.[12] Our study found that HVHF might play a beneficial effect on 7-day mortality and 28-day mortality in sample sizes <100, although all of the included trials reported that HVHF did not affect the incidence of mortality. One possible explanation for this discrepancy could be that the sample size was too small to show a clinical benefit, especially if event rates were lower than were expected. (Event rates had a broad 95% CI, indicating no statistically significant difference). Further, various disease status including septic shock, sepsis, ARDS, post-cardiac surgery shock, acute renal failure, acute kidney injury, and MODS contributes different mortality rate at specific follow-up periods, which was correlated with the power of pooled results.

Table 2

Sensitivity analysis for 28-day mortality.

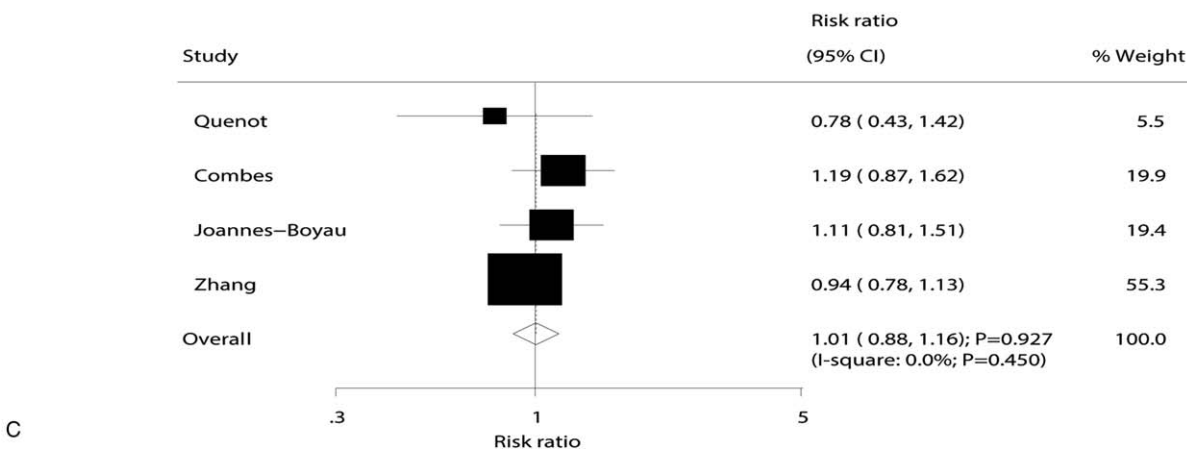| Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Quenot	0.94 (0.81–1.09)	.404	0.0	.759
Combes	0.91 (0.77–1.08)	.273	0.0	.685
Zhang	0.94 (0.81–1.10)	.434	0.0	.878
Peng	0.93 (0.80–1.08)	.357	0.0	.785
Bouman	0.93 (0.80–1.09)	.366	0.0	.685
Boussekey	0.93 (0.80–1.08)	.366	0.0	.713
Joannes-Boyau	0.93 (0.79–1.09)	.354	0.0	.667
Chu	0.93 (0.80–1.08)	.368	0.0	.732
Zhang	0.86 (0.68–1.07)	.181	0.0	.781
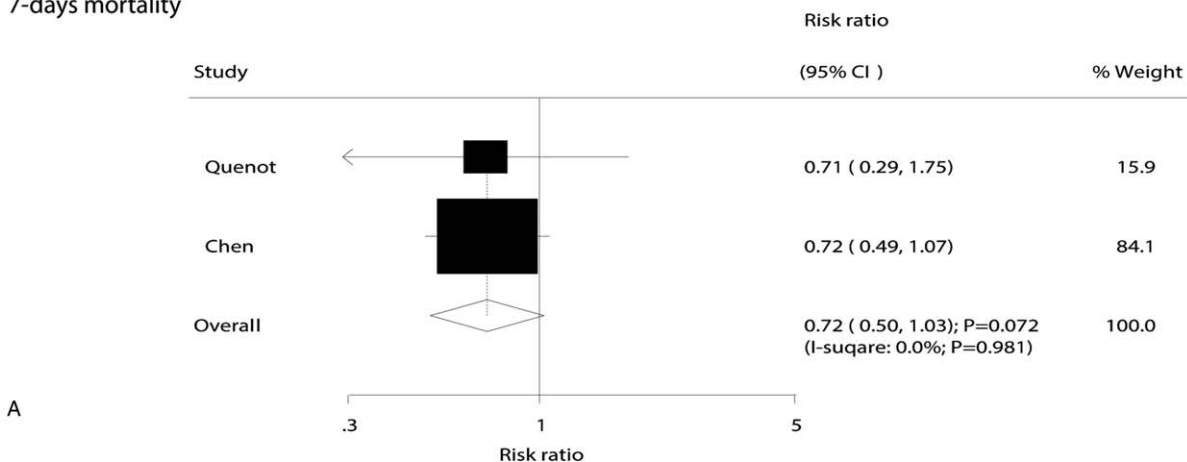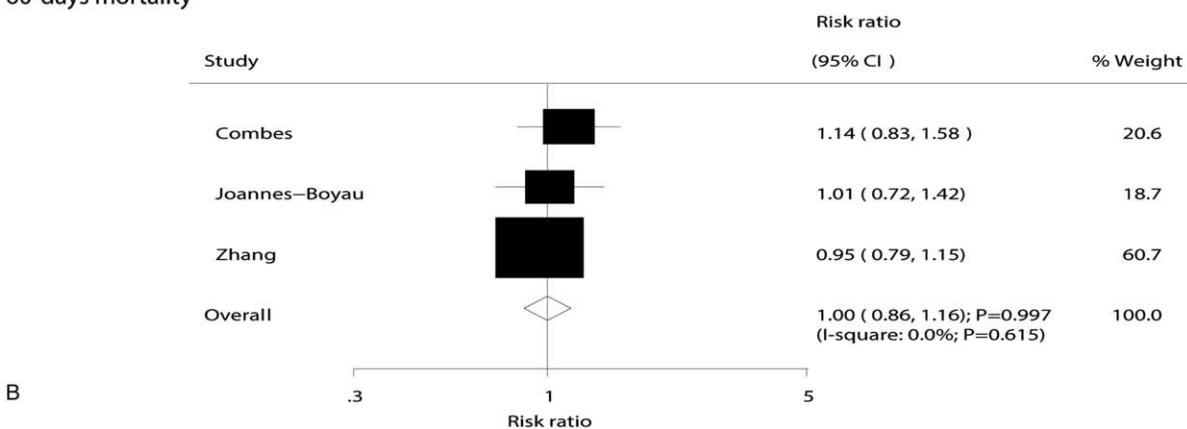
Figure 3. Effect of HVHF on the incidence of 7-days mortality (A), 60-days mortality (B), and 90-days mortality (C). HVHF = high-volume hemofiltration.

All of the included trials reported no significant effect of HVHF on mortality risk. Quenot et al[22] found that very HVHF using the Cascade system has no significant effect on the incidence of the need for catecholamines and no significant effect on mortality at 28 days in patients with septic shock. Combes et al[23] indicated that early HVHF did not lower 30-day mortality as compared with conservative strategy. Zhang et al[24] suggested that continuous HVHF would significantly improve pulmonary function, reduce the duration of mechanical ventilation, and

reduce the incidence of weaning from mechanical ventilation, while having no significant effect on mortality. Chen et al indicated that HVHF could lower levels of inflammation, improve oxygenation, reduce organ failure, and shorten duration of mechanical ventilation or length of hospital stays, while it have no significant effect on mortality.[25] Peng et al[26] found that pulse HVHF did not affect the incidence of mortality in patients with severe sepsis, although it effectively removed plasma cytokines. Further, survival at 28 days and recovery of renal

Table 3

Subgroup analysis for 28-day mortality.

Subgroup	RR and 95% CI	P value	Heterogeneity (%)	Between-subgroup heterogeneity
Publication year				
Before 2010	0.77 (0.41–1.43)	.403	0.0	0.530
2010 or after	0.94 (0.80–1.09)	.416	0.0	
Country				
Europe	0.91 (0.72–1.15)	.429	0.0	1.000
Asia	0.82 (0.55–1.23)	.330	17.9	
Sample size				
≥ 100	0.98 (0.83–1.15)	.804	0.0	0.055
< 100	0.64 (0.42–0.97)	.035	0.0	
Mean age				
≥ 60.0	0.84 (0.61–1.16)	.284	0.0	0.471
< 60.0	0.95 (0.80–1.13)	.577	0.0	
Percentage male (%)				
≥ 70.0	0.92 (0.67–1.25)	.578	0.0	1.000
< 70.0	0.93 (0.78–1.10)	.408	0.0	
Control				
Standard or low volume hemofiltration	0.96 (0.82–1.12)	.584	0.0	0.074
Conventional treatment	0.54 (0.29–1.01)	.053	0.0	
Study quality				
High	0.97 (0.74–1.27)	.819	0.0	1.000
Low	0.91 (0.76–1.09)	.298	0.0	

function were not improved using HVHF or early HVHF in patients with oliguric acute renal failure.[27] Boussekey et al[28] indicated that HVHF significantly reduced vasopressor requirements in septic shock patients with renal failure. Joannes-Boyau et al[29] suggested that HVHF did not affect the incidence of mortality and other secondary outcomes. Chu et al[30] concluded that pulse HVHF could reduce the levels of IL-6, IL-10 and TNF-α in patients with severe acute pancreatitis complicated with
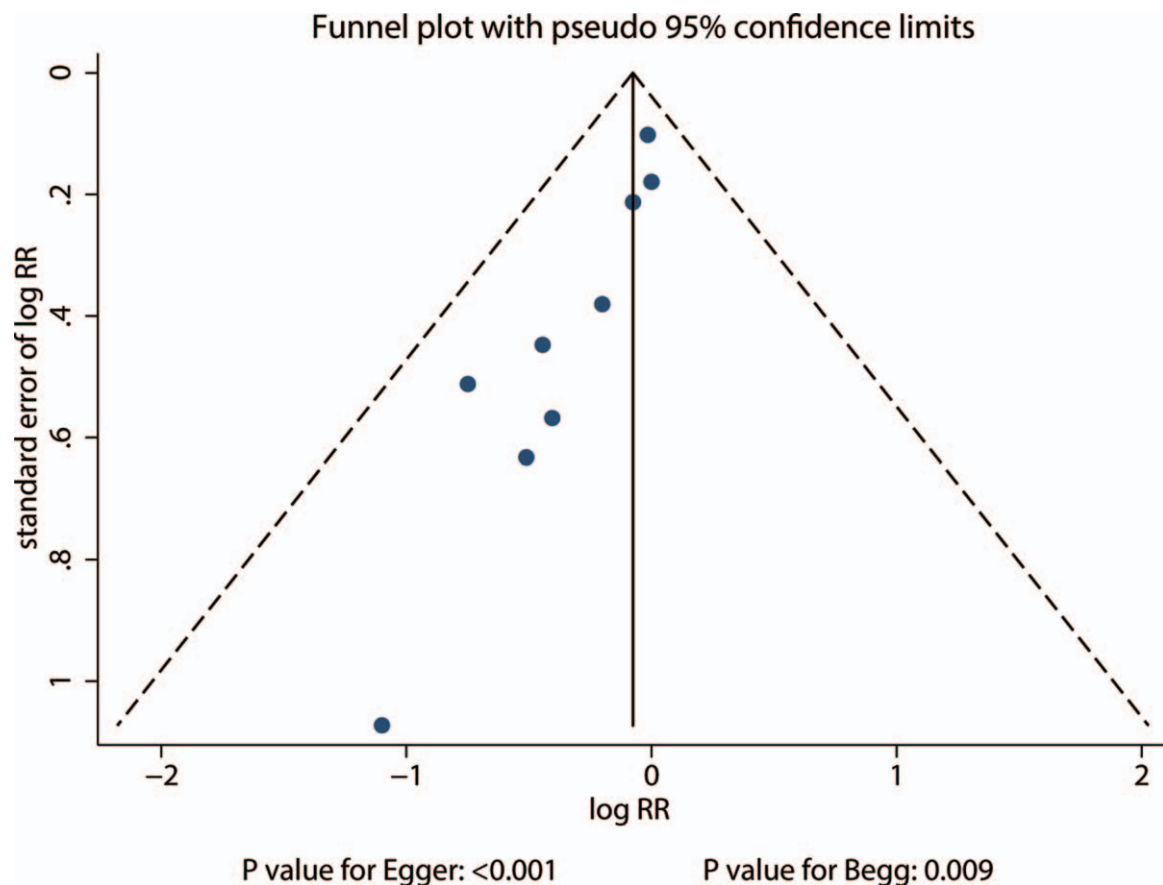

Figure 4. Funnel plot for 28-days mortality. HVHF = high-volume hemofiltration.

multiple organ dysfunction syndrome. Zhang et al[31] found that HVHF did not affect the incidence of mortality in patients with sepsis and acute kidney injury. Ghani et al found that HVHF could successfully remove some inflammatory cytokines in septic patients.[32] One cause for these significant differences could be that the populations studied were characterized by an unacceptably high attributable mortality, and the use of HVHF only applied in 11% to 22% of critically ill patients.[34,35]

Although the results of subgroup analysis in mostly subsets for 28-day mortality were consistent with overall results, we noted this conclusion was altering if pooled trials sample size < 100. Several reasons for this should be mentioned: mostly (7/11) of included trials sample size < 100, which contributed more robust result than contrary subset; The included 4 trials with >100 patients mainly focused in patients with post-cardiac surgery shock, ARDS, sepsis and AKI, and AKI. These diseases were contributed relative lower rate of mortality as compared other trials, which could affect the power to detect the difference between HVHF and usual care on the risk of mortality; Trials with large sample size were more latest, which published ranged from 2012 to 2015, more modern medical emergency approaches were used and correlated with lower rate of mortality as compared with contrary subset. Further, HVHF might superior than conservative therapy for reduced 28-day mortality risk. Although the pooled result was not associated with statistically significant, the reason for this could be only 3 trials included in this subset, and further large-scale prospective study to compare HVHF with conservative therapy for the risk of mortality at different follow-up periods.

Two strengths of our meta-analysis should be highlighted. First, only prospective RCTs were included, which could eliminate confounding bias when compared with observational studies. Second, the large sample size allowed us to quantitatively evaluate the effect of HVHF in treatment of critically ill patients on the incidence of mortality.

The limitations of our study should be mentioned: different characteristics of patients might result in biases; differences in diagnosis and reporting might have contributed to the differences in included trials; several trials with lower study quality were included, which might bias the results; and the analysis used pooled data (individual data were not available), which prevented us from performing a more detailed relevant analysis and obtaining more comprehensive results.

5. Conclusions

Overall, we note that treatment of critically ill patients with HVHF did not affect the incidence of 7-day, 28-day, 60-day, and 90-day mortality. Subgroup analysis indicated it might affect 28-day mortality if included trials had a sample size <100. Future large-scale RCTs should be conducted to verify the treatment effect of HVHF on mortality at different follow-up periods in critically ill patients.

Author contributions

Conceptualization: Yusheng Luo.
Data curation: Guijun Sun, Cailian Zheng, Yanling Li.
Investigation: Yuqiang Chen, Wei Zhang.
Project administration: Yusheng Luo, Juan Li.
Resources: Mei Wang, Jie Liu.
Validation: Cailian Zheng.
Writing – original draft: Yusheng Luo.
Writing – review & editing: Yusheng Luo.

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