Original Article

The therapeutic effect of high-volume hemofiltration on sepsis: a systematic review and meta-analysis

Fan Yin[1], Fang Zhang[1], Shijian Liu[2], Botao Ning[1]

[1]Department of Pediatric Intensive Care Unit, [2]Clinical Research Center, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China

Contributions: (I) Conception and design: B Ning, S Liu; (II) Administrative support: None; (III) Provision of study materials or patients: F Yin, F Zhang; (IV) Collection and assembly of data: F Yin, S Liu; (V) Data analysis and interpretation: F Yin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Botao Ning; Shijian Liu. Department of Pediatric Intensive Care Unit, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, 1678 Dongfang Road, Shanghai 200127, China. Email: ningbotao@126.com; liushijian@scmc.com.cn.

Background: Sepsis remains the leading cause of death in the intensive care unit (ICU), despite the treatment of sepsis has progressed. As a mode in continuous renal replacement therapy (CRRT), continuous veno-venous hemofiltration (CVVH) has been widely used in the treatment of sepsis. Whether high ultrafiltrate volume in CVVH is beneficial for sepsis survival remains controversial. We performed a systematic review and meta-analysis to evaluate the treatment effect of high-volume hemofiltration (HVHF) on sepsis.

Methods: A systematic search was conducted on the Medline, Embase, and Cochrane library to June 21, 2019, the keywords included "sepsis" "continuous blood purification" "continuous renal replacement therapy" "continuous veno-venous hemofiltration" and "continuous veno-venous hemodiafiltration". Summery statistic in this review was risk ratio (RR) and was performed by RevMan 5.2.

Results: Five randomized controlled trials (RCT) were included which contained 241 participants. Mortality related endpoints and other observations (length of stay, organ function evaluation, effect on hemodynamics, cytokine clearance and respiratory function) were used to assess the treatment effect of HVHF in sepsis. Three trials reported 28-day mortality, one of three trails also reported 60- and 90-day mortality; one trail did not specify the type of mortality; the fifth article reported hospital mortality. The pooled risk ratio for three trails of 28-day mortality was 0.96 (0.67, 1.38). Three trails reported length of stay related data. Four trails reported organ failure related scores. All trails reported the effect of HVHF on hemodynamics. Three trails reported cytokine clearance. Only two trails reported respiratory function related indicators. After analysis, the risk of bias in all trails was low.

Conclusions: The meta-analysis results suggested that treatment programs contained HVHF did not change the outcomes of patients with sepsis. So far, related studies on the use of HVHF in critically ill patients with sepsis or septic shock is rare. Researchers should consider additional large multicenter randomized controlled trials.

Keywords: Sepsis; high-volume hemofiltration (HVHF); risk ratio (RR); prognosis

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Introduction

Worldwide, 31.5 million cases of sepsis occur each year, resulting in 5.3 million deaths (1). Increasing incidence of sepsis has been observed in recent years. Although the treatment of sepsis has progressed, including early fluid resuscitation, antimicrobial therapy and mechanical ventilation, sepsis remains the leading cause of death in the intensive care unit (ICU) (1,2). Continuous renal replacement therapy (CRRT) which can precisely control fluid balance and remove metabolic waste has been widely used in the treatment of sepsis (3). Continuous veno-venous hemofiltration (CVVH) is one of the most commonly used modes. Convection is the main way to remove solutes in CVVH, it depends on the hydrostatic pressure on both sides of the membrane and accompanied by ultrafiltration (4). Whether high ultrafiltrate volume in CVVH is beneficial for sepsis survival than conventional volume hemofiltration (CVHF) is unclear. In addition, the definition of high volume during CVVH treatment remains controversial. In 2001, Ronco *et al.* proposed an ultrafiltrate volume of 20–35 mL/kg/h for traditional doses, >42.8 mL/kg/h as large doses (5); Bellomo *et al.* proposed to define ultrafiltrate volume >60 L/d as high-volume hemofiltration (HVHF) (6), Honore *et al.* recommended an ultrafiltrate volume >50 mL/kg/h as HVHF (7). In 2002, Acute Dialysis Quality Initiative (ADQI) defined ultrafiltrate volume >35 mL/kg/h as HVHF (8). In 2012, Joannes-Boyau *et al.* believed that HVHF meant continuous ultrafiltrate volume of >50 mL/kg/h for 24 h (9). But most articles in this field use 35 mL/kg/h as the definition of high volume in CVVH therapy. We intend to evaluate the effect of HVHF in sepsis by systematic review and meta-analysis.

Methods

Study search strategy

Investigators (F Yin, F Zhang) systematically and independently searched the Medline, Embase, Cochrane library databases to June 21 2019. The literature search included the keywords and MeSH terms "sepsis" "continuous blood purification" "continuous renal replacement therapy" "continuous veno-venous hemodiafiltration" and "continuous veno-venous hemofiltration" with no language restrictions.

Study selection

Investigators (F Yin, F Zhang) independently determined study eligibility by reviewing and retrieving the literatures by titles or abstracts, and subsequently the full texts. Different opinions on reviewing was resolved through consensus with an arbitrator (S Liu). The studies were included in this review if they met the following criteria: participants in studies are more than 18 years; study type is randomized controlled trail (RCT); a ultrafiltrate volume in interval group was greater than 35 mL/kg/h; the outcomes contained mortality; the sepsis meets the diagnostic criteria in the Society of Critical Care Medicine/European Society of Intensive Care Med/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society (SCCM/ESICM/ACCP/ATS/SIS) (10) or the Third International Consensus Definitions for Sepsis and Septic Shock (11). Studies were excluded if non-sepsis patients included in the study; treatment type is not CVVH, such as: continuous veno-venous hemodiafiltration (CVVHDF); duplicate articles described in the same study.

Data extraction and quality assessment

Two reviewers (F Yin, F Zhang) independently extracted data elements from each trial, including patients baseline characteristics, study characteristics and CRRT intervention, mortality related endpoints and other endpoints. We contacted the author of the paper to confirm unclear data. We used RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Demark) to assess risk of bias and quality of each included literatures. Through the authors judgement, we clarified the risk of bias as "low" "high" or "unclear". Publication bias was detected by visual symmetry of funnel plots, with asymmetry suggesting possible publication bias. This study was approved by the ethical committee of Shanghai Children's Medical Center. The approval number is SCMCIRB-W2020001.

Statistical analysis

We enrolled and analyzed data using RevMan 5.3 software.

We used risk ratio (RR) with 95% confidence interval (CI) for the statistical analysis of dichotomous data, summary statistic in this review was performed using a forest plot. Heterogeneity was assessed by the P value and the I-square statistic (I^2) in the pooled analyses, which represents the percentage of total variation across studies (12). If the P value was less than 0.1 or the I^2-value was greater than 50%, the summary estimate was analyzed in a random-effects model. Otherwise, a fixed-effects model was applied.

Results

Study characteristics and quality assessment

We found 1,728 relevant literatures in the initial search from Medline and Embase, of which 225 were excluded because of duplication. Of the remaining 1,503 studies, 1,402 were excluded after reviewing the titles and abstracts. After reviewed the full texts, 86 studies were excluded in accordance to the eligibility criteria. Eligibility of the remaining 15 studies was assessed. Among these, 5 studies that included 241 patients published between 2006 and 2016 were included for meta-analysis for efficacy assessment of HVHF in septic patients. Literature screening strategies was showed in a flowchart (*Figure 1*). The included studies were geographically diverse: one study was conducted in America, one in Australia, two in Europe, and the remaining one in Asia. We used the mortality related endpoints as an indicator of the efficacy of HVHF. Characteristics of the enrolled studies such as trail design, type of anticoagulation, ultrafiltrate volume and ultrafiltrate volume were presented in *Table 1*. Patient baseline characteristics were shown in *Table 2*.

Our meta-analysis was concentrating on the effect of HVHF in sepsis. Fifteen clinical trials were identified, only five of them qualifying for quantitative synthesis. Piccinni *et al.* in 2006 (13) and Cui *et al.* in 2015 (14) were excluded because there were observation studies; Ronco *et al.* in 2000 (15), Vesconi *et al.* in 2009 (16), Palevsky *et al.* in 2008 (17) were not included because the participants enrolled were not all sepsis patients. The record from Honore *et al.* in 2000 (7), Joannes-Boyau *et al.* in 2004 (18), Cornejo *et al.* in 2006 (19) had to be excluded because there were single arm trails. Due to conducting blood purification without HVHF, Mayumi *et al.* in 2016 (20) were excluded after reviewing. Zhang *et al.* in 2012 (21) compared the impact of HVHF (50 mL/kg/h) and extra HVHF (85 mL/kg/h) on sepsis, which didn't meet our inclusion criteria.

We have evaluated the risk of bias and quality of each literatures. *Figure 2* showed the results of enrolled literature quality evaluation. In the random sequence generation, all studies were at low risk of selection bias; in the allocation concealment, three studies had low risk of bias, one study (22) (Ghani *et al.* in 2006) had unclear risk of bias due to insufficient information available, another (23) (Boussekey *et al.* in 2008) had high risk of bias because of the randomized group for the last participant in each block was known in advance; in blinding of participants and personnel, four studies were at low risk, one study (24) (Chung *et al.* in 2017) had high risk of bias because of open-label trials; in blinding of outcome assessment, one study were at low risk, while remaining study (22-25) had unclear risk due to insufficient information available; in incomplete outcome data, two studies had low risk of bias, three studies (9,22,23) had unclear risk of bias because relevant data was not available from the original text and trial registration website. Only one study (23) had unclear risk of reporting bias. Publication bias was detected by visual symmetry of funnel plots. In the evaluation of mortality related endpoints, a total of 3 studies were included. Asymmetry suggesting possible publication bias, the funnel plot (*Figure 3*) showed no obvious asymmetrically, we thought there was no potential publication bias.

Mortality related endpoints

Joannes-Boyau *et al.* (9), Boussekey *et al.* (23) and Chung *et al.* (24) reported 28-day mortality, the pooled risk ratio (RR) for the three trails of 28-day mortality was 0.96 (0.67, 1.38). *Figure 4* represented the pooled results of 28-day mortality. Due to small sample size, it was difficult to perform a summary analysis of all mortality related endpoints. Joannes-Boyau *et al.* (9) also reported 60-day mortality (49% in CVHF, 50% in HVHF) and 90-day mortality (50.7% in CVHF, 56% in HVHF). Ghani *et al.* (22) reported a mortality of 76% (25/33), but the type of mortality was unknown. Cole *et al.* (25) used a cross-over design and reported hospital mortality of 54.5% (5/11). All mortality related endpoints of enrolled studies were presented in *Table 3*.

Other endpoints

Except for mortality related endpoints, enrolled studies also reported other endpoints including length of hospital/ICU stay, organ function assessment, hemodynamic changes and

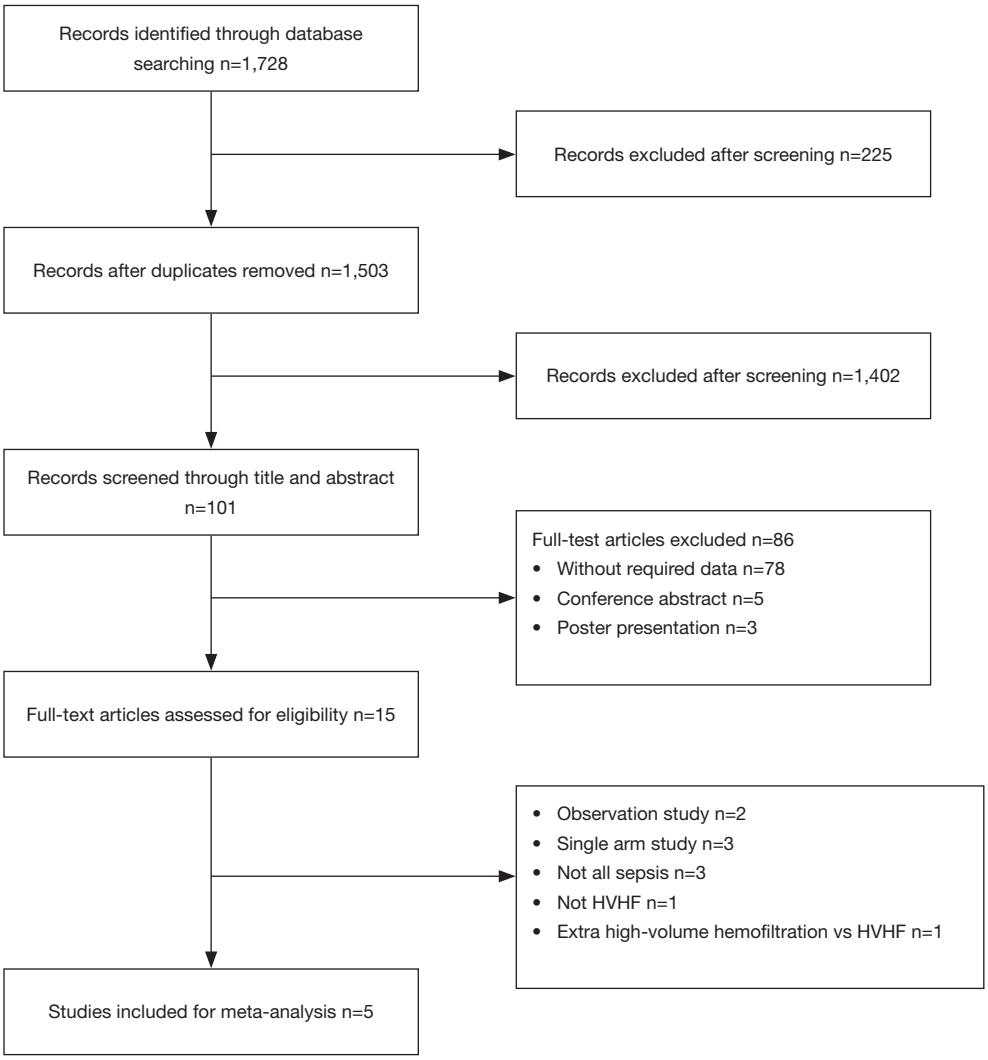

Figure 1 Study selection flow diagram.

cytokine clearance. The incomplete data of the enrolled studies resulted in difficulty in pooling estimates for these endpoints. All these endpoints were shown in *Table 4*.

Length of stay

Three studies investigated the length of stay. Among then, Boussekey *et al.* (23) and Chung *et al.* (24) recorded the length of ICU stay. Joannes-Boyau *et al.* (9) reported the ICU-free day. Both groups in the three studies showed no significant difference in the length of stay.

Organ function evaluation

Four studies evaluated the organ function through critical illness scores. Ghani *et al.* (22) measured Sequential Organ Failure Assessment (SOFA) scores at day 0, 1 and 7. SOFA scores at baseline were similar between the two treatment groups. Both groups showed a significant reduction in the SOFA scores at day 7 compared to baseline (HVHF,

Table 1 Study characteristics and CRRT intervention

Study	Sample size	Country/ area	Trail design	Anti-coagulation	Ultrafiltrate volume (mL/kg/h)	Membrane materials of filter	CRRT duration	Frequency of filter change	molecular weight cut-off (kDa)	Replacement fluid (% prefilter/% postfilter)
Joannes-Boyau *et al*., 2013	140	Belgium, France, Netherland	Parallel group	UFM	35 (CVHF), 70 (HVHF)	PES	96 hours	48 hours	35	33.3/66.7
Boussekey *et al*., 2008	20	France	Parallel group	Heparin	35 (CVHF), 65 (HVHF)	PES	4 days (max)/ without NE for at least 4 hours	Daily/ obstructed	20	33.3/66.7
Ghani *et al*., 2006	33	Malaysia	Parallel group	Heparin or no anticoagulation	35 (CVHF), 100 (HVHF)	PES	6 hours	NR	35	50/50
Chung *et al.,* 2017	37	USA	Parallel group	Trisodium citrate/heparin	20–35 (CVHF), 70 (HVHF)	NR	48 hours	NR	NR	NR
Cole *et al*., 2001	11	Australia	Cross-over design	Heparin	1 L/h (CVHF), 6 L/h (HVHF)	AN69	8 hours (CVHF) + 8 hours (HVHF)	NR	NR	33.3/66/7

NR, not reported; CRRT, continue renal replacement treatment; HVHF, high-volume hemofiltration; CVHF, conventional volume hemofiltration; UFM, unfractionated heparin; PES, poly-ethersulfone; NE, norepinephrine.

Table 2 Patient baseline characteristics

Study	Subjects	Admission diagnosis	CVHF			HVHF		
			Mean age (years)	Male sex, n [%]	Critical scores	Mean age (years)	Male sex, n [%]	Critical scores
Joannes-Boyau *et al*., 2013	Sepsis with AKI	Non-operative (infection)	70 (58 to 75)	38 [54]	SOFA: 12 (10 to 14); SAPS II: 64 (52 to 74)	68 (58 to 77)	45 [68]	SOFA: 12 (11 to 14); SAPS II: 68 (59 to 78)
Boussekey *et al*., 2008	Septic shock	Non-operative (infection)	72.55 (54 to 77)	8 [80]	SAPS II: 67 (61 to 75); Apache II: 33.5 (28 to 37)	68 (58 to 74)	7 [77.8]	SAPS II: 66 (56 to 69); Apache II: 31 (26 to 33)
Ghani *et al*., 2006	Sepsis & septic shock	Operative (med. surgery/ trauma)	57.5 (21 to 74)	11 [61.1]	NR	58 (26 to 79)	8 [53.4]	NR
Chung *et al*., 2017	Septic shock with AKI	Non-operative (burn)	47 (37 to 62)	NR [75.6]	MODS: 10 (9 to 12); APACHE II: 32 (24 to 35)	50 (42 to 60)	NR [73.9]	MODS: 10 (7 to 14); APACHE II: 28 (25 to 34)
Cole *et al*., 2001	Septic shock	Non-operative (infection)	67 (58 to 69)	8 [72.7]	APACHE: 25; SAPS II: 50	–		–

All variables in this table are reported as median (1st to 3rd quartile). NR, not reported; HVHF, high-volume hemofiltration; CVHF, conventional volume hemofiltration; AKI, acute kidney injury; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; MODS, multiple organ dysfunction syndrome; APACHE II, acute physiology and chronic health evaluation.

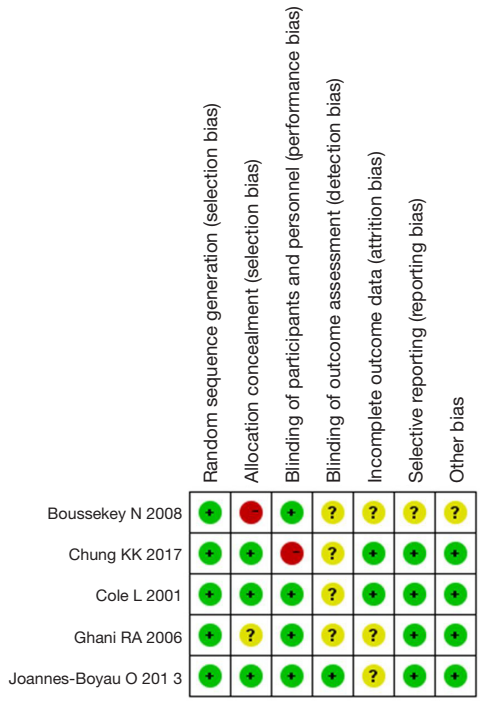

Figure 2 Results of literature quality assessment.

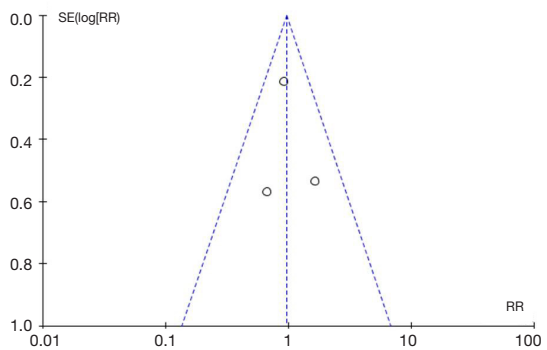

Figure 3 The funnel plot of the publication bias analysis.

P=0.048; CVHF, P=0.006). Chung *et al.* (24) found MODs scores decreased significantly in the HVHF group when compared to the day of treatment initiation (P=0.02). Both Ghani *et al.* (22) and Chung *et al.* (24) did not report the results of comparation between groups (CVHF and HVHF).

SOFA scores and simplified acute physiology score (SAPS) II scores at days 4 and 28 in the study of Joannes-Boyau *et al.* (9) showed no significant difference between two groups. This goes along with the finding of Boussekey *et al.* (23), who found no significant difference of logistic organ dysfunction (LOD) scores between two groups.

Effect on hemodynamics

All studies evaluated the effect on hemodynamics changes after intervention. Except for studies of Boussekey *et al.* (23), the remaining studies did not reported the hemodynamic changes between groups. Boussekey *et al.* (23) could not detect a difference of mean arterial pressure (MAP) in both groups. Only Chung *et al.* (24) reported a significant reduction of vasopressor dependency index (VDI) in HVHF group compared to baseline. Other studies failed to find differences on hemodynamic metrics including MAP in both groups compared to baseline.

Cytokine clearance

Among the included studies, 3 studies measured serum cytokine levels. The results of comparation between groups (CVHF and HVHF) were showed below. Ghani *et al.* (22) could not detect a difference of interleukin (IL)-6 level between two groups, while the HVHF group demonstrated a reduction of the serum IL-1-ra levels compared with an increase in the CVHF group (3 h, P=0.007; 6 h, P=0.036). In the study of Chung *et al.* (24), the levels of IL-6, IL-8, IL-10, IL-12, interferon (IFN)-γ and tumor necrosis factor (TNF)-α were measured over the intervention period, no cytokines showed difference at each time point between the two groups. This goes along with the finding of Cole *et al.* (25), who found no significant reduction of complement C3a, C5a, IL-10, IL-8, TNF-α levels between two groups. In contrast, Chung *et al.* (24) could not detect any reduction in IL-6, IL-8, IL-10, IL-12, IFN-γ and TNF-α in both groups at all time points compared to baseline.

The results of comparation within groups (CVHF and HVHF) were showed below. Cole *et al.* (25) discovered significant lower level of IL-6 at 6 hours HVHF group compared to baseline. This goes along with the finding of Ghani *et al.* (22), who found a significant decrease of IL-8, TNF-α levels (P<0.01) only in patients treated with HVHF. But Chung *et al.* (24) found there were no significant

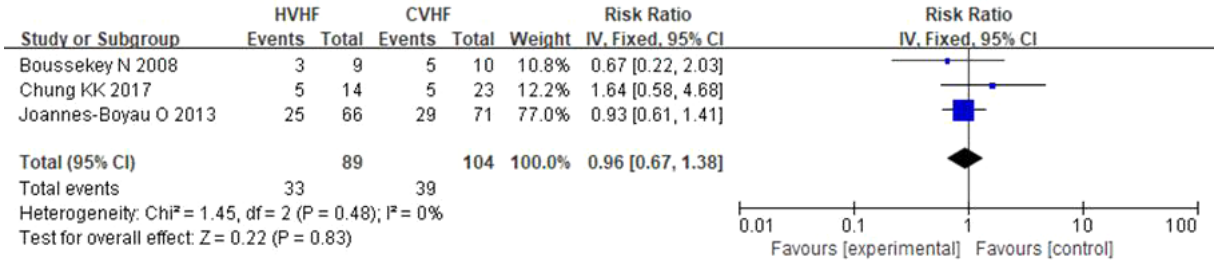

Figure 4 Forest plot of comparison in relative risk of mortality.

Table 3 Mortality related endpoints

Study	Mortality related endpoints	CVHF		HVHF	
		Death	Total	Death	Total
Joannes-Boyau *et al*., 2013	28-/60-/90-day mortality	29 (28-day); 35 (60-day); 36 (90-day)	71	25 (28-day); 33 (60-day); 37 (90-day)	66
Boussekey *et al*., 2008	28-day mortality	3 (28-day)	9	5 (28-day)	10
Ghani *et al*., 2006	Unknown type of mortality	25/33 (76%)			
Chung *et al*., 2017	28-day mortality	5	14	5	23
Cole *et al*., 2001	Hospital mortality	5/11 (54.5%)			

reduction in IL-6, IL-8, IL-10, IL-12, IFN-γ levels at all time points in both groups compared to baseline.

Respiratory function

Only Joannes-Boyau *et al.* (9) and Boussekey *et al.* (23) reported metrics in respiratory function. The former evaluated partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2), the latter investigated ((PaO_2/FiO_2) and duration of mechanical ventilation. Both studies found no significant difference in respiratory function metrics.

Discussion

Sepsis, especial septic shock, remains the leading cause of death in ICU, which is associated with patients' poor prognosis (26). 3.0 version of sepsis definition emphasizes the importance of organ dysfunction in the pathogenesis of sepsis (27). CRRT may improve organ function in patients with sepsis (28). CVVH is a commonly used mode in clinical CRRT treatment. Ultrafiltrate volume is the key to CVVH treatment in patients with sepsis. Whether high ultrafiltrate volume in CVVH is beneficial for sepsis survival remains controversial. RCTs included in this meta-analysis have different cut-off in definition of high-volume. A conventional-volume hemofiltration would be 20–25 mL/kg/h of effluent generation (28). In HVHF, the ultrafiltration volume is greater than 35 mL/kg/h (15). We continued renal replacement therapy and chose 35 mL/kg/h as thresholds to distinguish the CVHF and HVHF.

Due to different formats for reporting mortality, not all RCTs are included in the pooled analysis. The pooled RR of three trails (Joannes-Boyau *et al.* in 2013, Boussekey *et al.* in 2008, Chung *et al.* in 2017) failed to show improvement in 28-day mortality for patients with sepsis. No overall beneficial effects of HVHF compared to CVHF can be detected. Till now, few studies have focused on how HVHF affected the outcomes of sepsis. Only Emj *et al.* (29) investigate the impact of HVHF in critically ill patient in 2013 and updated the contents in 2016 (30), and got the similar results as we reported after 3 years period.

We also evaluated the effect on other endpoints of patients with HVHF intervention, including length of stay, organ function evaluation, effect on hemodynamics, cytokine clearance, respiratory function. Because of poor data consistency, we only describe the relevant endpoints.

Some trails showed that HVHF could improve organ

Table 4 Other endpoints

Study	HVHF compared to CVHF				
	Length of stay	Organ function evaluation	Effect on hemodynamics	Cytokine clearance	Respiratory function
Joannes-Boyau *et al*., 2013	n.s. diff. in ICU-free days (day 90) and Hospital-free days (day 90) between both groups	n.s. diff. in SOFA scores and SAPS II scores (day 4, day28) between both groups	NR between both groups; n.s. diff. of MAP, SVRI, VDI (day 4) compared to baseline in both groups	NR	n.s. diff. in PaO_2/FiO_2 (day 4) between both groups
Boussekey *et al*., 2008	n.s. diff. in length of ICU stay between both groups	n.s. diff in LOD scores between both groups	n.s. diff. in MAP between both groups	NR	n.s. diff. in PaO_2/FiO_2 and duration of mechanical ventilation between both groups
Ghani *et al*., 2006	NR	NR between both groups; sign. reduction of SOFA score (day 7) compared to baseline in both groups	NR between both groups; n.s. diff. of MAP, DBP, SBP compared to baseline in both groups	n.s. diff in IL-6 level between both groups at all time points; sign. diff in IL-1ra level between both groups; sign. reduction of IL-6 level (6 hours) in HVHF group compared to baseline	NR
Chung *et al*., 2017	n.s. diff. in ICU days among survivors between both groups	NR between both groups; sign. reduction of MODS score (day 14) in HVHF group	NR between both groups; sign. reduction of VDI in the HVHF group compared to baseline; n.s. diff. of MAP compared to baseline in both groups	n.s. diff. in IL-6, IL-8, IL-10, IL-12, IFN-γ level between both groups at all time points; n.s. reduction in IL-6, IL-8, IL-10, IL-12, IFN-γ level in both groups at all time points compared to baseline	NR
Cole *et al*., 2001	NR	NR	NR between both groups; n.s. diff. of MAP, CVP, CI and PAWP compared to baseline in both groups	n.s. reduction of C3a, C5a, IL-10, IL-8, TNF-α level from baseline between both groups; sign. changes of C3a, C5a, IL-10 level compared to baseline in both groups; sign. changes of IL-8, TNF-α level compared to baseline in HVHF group	NR

NR, not reported; ICU, intensive care unit; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; LOD, logistic organ dysfunction; MODS, multiple organ dysfunction syndrome; SVRI, systemic vascular resistance index; ASAT, aspartate aminotransferase; VDI, vasopressor dependency index; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; n.s. diff., no significant difference; sign., significant difference.

function in patients of different ages (24,31). But in this meta-analysis, most other endpoints of enrolled studies didn't show any significant differences between CVHF and HVHF. Some interventions show differences only when compared to baseline. Moreover, for the same endpoint, the results reported by each study differed greatly. In addition to the hemofiltration volume, the pre/post dilution ratio, and the blood flow volume can affect the trail results, thereby changing the conclusion of the meta-analysis.

There are some side-effects, such as bleeding, infection,

thrombosis and thrombocytopenia. Few literatures included in this review reports HVHF related adverse events, only Joannes-Boyau 2013 described adverse events but didn't assess whether they were directly related to HVHF. Moreover, HVHF has been widely used in the treatment of acute kidney injury (AKI) with few side effects. In addition, membrane materials for filter were constantly updated which avoid the occurrence of side effects. The safety of HVHF has been confirmed.

It is worth noting that due to lack of relevant clinical trials, pooled results come from only 5 RCTs including 241 participants (small sample size). Enrolled RCTs used different assessment methods, which lead to different participant's condition. Additionally, the median age of participants exceeded 50 years old and lack of data on youth and children, which failed to fully reflect differences in response to treatment for patients of different ages. In addition, different maintenance time and filter of HVHF may affect the outcomes of sepsis patients. Attention should be paid to the generalization of conclusions because the limitation of the evidence. More trials with larger sample sizes and high-quality evidence are needed.

Conclusions

The available evidence on ultrafiltrate volume does not indicate effectiveness of HVHF in patients with sepsis, HVHF may be effective in improving some secondary endpoints other than mortality. But the use of HVHF is safe for sepsis patients. More larger sample sizes trails crossing all ages are needed to supplement the defects of the existing evidence.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.48). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethical committee of Shanghai Children's Medical Center (SCMCIRB-W2020001).

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