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# Effect of High-Volume Hemofiltration in Critically Ill Patients: A Systematic Review and Meta-Analysis

Authors' Contribution:  
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 Data Interpretation D  
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**Background:** Studies have been carried out to assess the efficacy of high-volume hemofiltration (HVHF) among critically ill patients. However, it is currently unclear whether HVHF is really valuable in critically ill patients.

**Material/Methods:** Randomized controlled trials evaluating HVHF for critically ill adult patients were included in this analysis. Three databases were searched up to July 27, 2018. The relative risk (RR), mean difference (MD), and 95% confidence intervals (CI) were determined.





**Results:** Twenty-one randomized controlled trials were included in this analysis. Overall, HVHF was associated with lower mortality compared with control measures (RR=0.88, 95% CI=0.81 to 0.96, P=0.004) in critically ill patients. Sub-analysis revealed HVHF reduced mortality in sepsis and acute respiratory distress syndrome patients, but no similar effect in other diseases. HVHF decreased levels of plasma tumor necrosis factor and interleukin 6. The heart rate of the HVHF group after treatment was slower than the control group, while we found higher mean arterial pressure in the HVHF group, but oxygenation index was not significantly different between the two groups. HVHF had no remarkable influence on acute physiological and chronic health evaluation score (APACHE II score) compared with the control group.

**Conclusions:** HVHF might be superior to conventional therapy in critically ill patients.

**MeSH Keywords:** **Critical Illness • Hemofiltration • Randomized Controlled Trial • Treatment Outcome**

**Abbreviations:** **RCTs** – randomized controlled trials; **HVHF** – high volume hemofiltration; **ARDS** – acute respiratory distress syndrome; **ICU** – Intensive Care Unit; **MAP** – mean arterial pressure; **TNF** – tumor necrosis factor; **IL-6** – interleukin-6; **HR** – heart rate; **OI** – oxygenation index; **APACHE II score** – acute physiological and chronic health evaluation score; **RR** – relative risk; **CI** – confidence interval; **MD** – mean difference; **IQR** – interquartile range; **SD** – standard deviation

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## Background

Hemofiltration was firstly described by Kramer in 1977 for the treatment of fluid overload patients resistant to diuretics [1]. Clinical practice for more than 30 years has shown that hemofiltration can effectively improve the prognosis (including mortality, length of hospital stays) of critically ill patients [2,3]. At present, it has become a common therapeutic tool in the intensive care unit (ICU).

In 1992, Grootendorst et al. [4] put forward the concept of high-volume hemofiltration (HVHF) on the basis of continuous veno-venous hemofiltration (CVVH), and for the first time in a porcine model of sepsis. HVHF was found to be effective in improving hemodynamic parameters (including cardiac output and blood pressure). In another study, Grootendorst et al. [5], injected the ultrafiltration fluid from septic pigs into healthy pigs; after the infusion was finished, the hemodynamic parameters of healthy pigs deteriorated. However, if the ultrafiltration was injected from healthy pigs, there was no such phenomenon. Thus, they hypothesized that HVHF worked by removing certain substances that could induce cardiac dysfunction and vasodilatation in septic animals. Subsequently, Rogiers et al. [6] and Bellomo et al. [7] also confirmed the ability of HVHF to improve hemodynamic parameters in septic animal models.

The findings of animal experiments have attracted a great deal of interest in the potential advantages of HVHF in human. Ronco et al. [8] reported for the first time in 2000 that HVHF can reduce the mortality of critically ill patients, including sepsis, severe trauma, and postoperative patients. In addition, other researchers further supported that the use of HVHF was associated with improvement prognosis of patients with acute respiratory distress syndrome (ARDS) [9] and acute renal injury [10]. New studies published in 2018 also showed HVHF effectively reduced mortality in critically ill patients with severe burn [11] and severe acute pancreatitis (SAP) [12]. However, a multicenter study (IVOIRE study) published in 2013 by Joanne-Boyao et al. [13] suggested there was no evidence that HVHF reduced 28-day mortality or contributed to early improvements in hemodynamic parameters or organ function. The study by Ghani et al. [14] and Boussekey et al. [15] also failed to find the benefits of HVHF in critically ill patients. Therefore, it is still controversial whether application of HVHF can really improve the condition of critically ill patients. In this meta-analysis, we developed a unified standard to systematically evaluate the clinical effect of HVHF on critically ill patients.

## Material and Methods

### Literature search strategy

According to the criteria of literature inclusion and exclusion, 2 researchers searched the literatures of PubMed, Cochrane, and Embase databases independently. The retrieval time was from the inception of databases to July 27, 2018. Languages were not restricted. The search was performed using the following items: "randomized", "clinical trial", "renal replacement therapy", "high volume hemofiltration", "intensity", "intensive care unit", "critically ill", "critical illness". Disagreements of study research were resolved by discussions, when discussions failed to resolve a disagreement, a third author was involved to make the decision.

### Eligibility criteria

Eligibility criteria included: 1) publicly published randomized controlled trials (RCTs) that reported HVHF use in critically ill adult patients; 2) outcome indicators included 1 of the following items: mortality, serum levels of tumor necrosis factor (TNF) and interleukin-6 (IL-6), heart rate (HR), mean arterial pressure (MAP), oxygenation index (OI), acute physiological and chronic health evaluation score (APACHE II); 3) a clear time and location for the studies to be conducted; 4) sample size of treatment group and control group was clear and definite; 5) dosage and duration of treatment in HVHF group and the treatment measures in the control group was provided in original articles; and 6) baseline level of 2 groups were comparable.

### Exclusion criteria

Exclusion criteria included exclusion of non-RCTs, case reports, animal studies, reviews, letters, duplicated data, and non-adult studies.

### Data extraction

Data from the included RCTs was extracted by 2 authors independently, if there was any disagreement, the third author was invited to discussion and consensus. Self-made data extraction table was used to extract data, For each study, the following information was extracted: 1) the basic situation of studies: name of first author, publication year, the country, etc.; 2) baseline characteristic of patients: sample size, disease types, etc. 3) intervention measures: dose of ultrafiltration rates used in HVHF group and specific treatment measures in control group; 4) outcome indicators: mortality, serum levels of TNF and IL-6, HR, MAP, OI, and APACHE II score.

**Methodological quality assessment**

All studies were evaluated by 3 reviewers independently for methodological quality assessment by using the Cochrane risk of bias tool which includes the following 7 aspects: random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The assessment criteria were as follows: high risk bias was any aspect aforementioned here that was regarded as high risk; low risk bias was all the aspects were of low risk; and unclear risk bias was unclear risk in any aspect while no high risk in other aspects.

**Statistical analysis**

Data analysis was performed by using ReviewManager 5.3 software provided by the Cochrane International Cooperation organization. Using 2-sided tests, the level of significance was 0.05, with  $P < 0.05$  in 2-sided tests considered as statistically significant. Metrological data (TNF, IL-6, HR, MAP, OI, APACHE II score) was analyzed with mean deviation (MD) and standard deviation (SD), and counting data (mortality) was analyzed with relative risk (RR) and 95% confidence intervals (95% CI) as effect statistic. If there was no significant heterogeneity ( $I^2 < 50\%$ ,  $P > 0.05$ ), using the Peto Mantel-Haenszel fixed effect model, if the heterogeneity test was significant ( $I^2 \geq 50\%$ ,  $P < 0.05$ ), the Dersimonian Laird random effect model was used. Reverse funnel plot was used to analyze potential publication bias, if the number of studies included was large enough. Sensitivity analysis was adopted to detect the effect of each study on the overall estimate by using the leave-one-out approach when necessary.

**Results**

**Literature retrieval results**

A total of 282 potential studies (110 through PubMed, 133 through Embase, and 39 through the Cochrane Library) were screened according to the search strategy, and no other articles were found through manual searches. Then 136 records that remained after 146 records were removed as duplicates. After screening of the titles and/or abstracts, 112 citations were discarded for reasons shown in Figure 1. Consequently, 24 full-text articles were assessed for eligibility, and 3 articles were excluded for lacking relevant outcome indicators, 21 articles with 3135 critically ill patients (1610 in HVHF group and 1525 in control group) were included in the final meta-analysis. The flow chart for detailed search steps is presented in Figure 1.

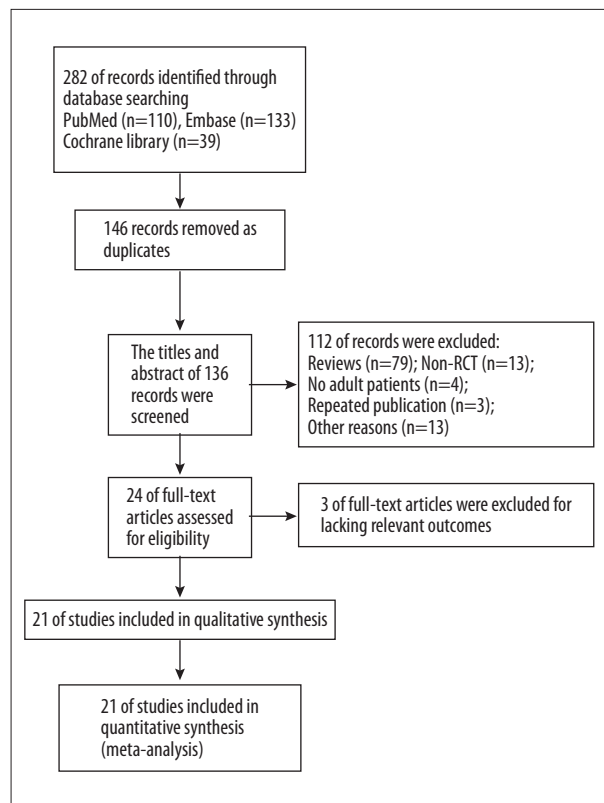


Figure 1. PRISMA flow diagram of the study selection process.

**Basic characteristics of the included studies**

The key baseline characteristics are illustrated in Table 1. The 21 studies included were published from 2000 to 2018; all of the studies were RCTs, 4 studies were multicenter trials [13,16–18], and the studies’ population included Asian, European, and American. Among 21 studies, 8 studies enrolled septic patients [13–17,19–21], 5 studies recruited patients with SAP [22–26], 3 studies recruited patients with ARDS [9,27,28], acute kidney injury (AKI) patients were included in 3 studies [8,29,30], 2 studies respectively reported on patients with severe burn [11] and postcardiac surgery shock [18]. For outcomes, 17 assessed mortality [8,9,11,13,15–19,21–24,26, 28–30], 4 assessed TNF [9,20,25,27], 2 assessed IL-6 [19,25,27], 5 assessed HR [14,20,22,26,28], 3 assessed MAP [14,26,28], 5 assessed OI [9,20,26–28], and 5 evaluated APACHE II score [20,22,23,26,27].

**Assessment of study quality**

After the methodological quality assessment of 21 included studies, no study was judged to be at low risk of bias, 8 studies [15–17,21,23,26,27,30] were regarded to be high risk bias for at least 1 high risk item, and the risk of bias was unclear for the remaining 13 studies [8,9,11,13,14,18–20,22,24,25,28,29] (detailed in Figure 2).

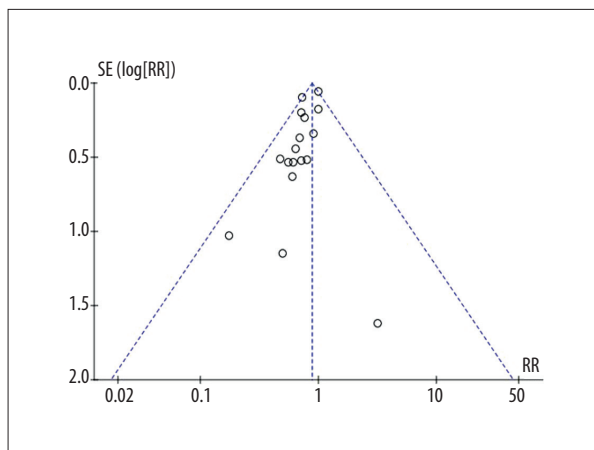
**Table 1.** The basic characteristics of studies included.

Study	Location	Number of patients (HVHF/Control)	Centers	Population	Intervention measures		Outcome
					HVHF	Control	
Bellomo R [30] (2009)	Australia+ New Zealand	1464 (721/743)	2	Acute renal failure	40 ml/kg/h	25 ml/kg/h	Mortality
Bo You [11] (2018)	China	82 (41/41)	1	Burns >50% TBSA	65 ml/kg/h	Conventional therapy	Mortality
Bouman CS [29] (2002)	Netherlands	106 (35/71)	1	Acute renal failure	72–96L per day	24–36L per day	Mortality
Boussekey N [15] (2008)	France	19 (9/10)	1	Sepsis	65 ml/kg/h	35 ml/kg/h	Mortality
Chen X [9] (2014)	China	105 (55/50)	1	ARDS	6 L/h	Conventional therapy	Mortality, OI, TNF
Chu LP [22] (2012)	China	30 (15/15)	1	Pancreatitis	85 mL/kg/h	35 mL/kg/h	Mortality, APACHE II
Chung KK [16] (2017)	USA	37 (23/14)	Multicenter	Sepsis	70 ml/kg/h	20–35 ml/kg/h	Mortality
Combes A [18] (2015)	France	224 (112/112)	Multicenter	Postcardiac surgery shock	80 ml/kg/h	<35 ml/kg/h	Mortality
Ghani RA [14] (2006)	Malaysia	33 (15/18)	1	Sepsis	100 ml/kg/h	35 ml/kg/h	MAP, HR
Gou J [19] (2017)	China	22 (11/11)	1	Sepsis	60 ml/kg/h	Conventional therapy	Mortality, IL-6
He WH [23] (2016)	China	66 (33/33)	1	Pancreatitis	50 mL/kg/h	Conventional therapy	Mortality, APACHE II
Hu D [20] (2012)	China	14 (7/7)	1	Sepsis	6 L/h	CPFA	MAP, HR, OI, TNF, APACHE II
Jiang HL [24] (2005)	China	37 (18/19)	1	Pancreatitis	4 L/h	1 L/h	Mortality
Joanne-Boyao O [13] (2013)	France+ Belgium+ Netherlands	137 (66/71)	Multicenter	Sepsis	70 mL/kg/h	35 mL/kg/h	Mortality
Liu C [25] (2017)	China	86 (43/43)	1	Pancreatitis	35 mL/kg/h	20 mL/kg/h	IL-6, TNF
Peng Z [21] (2010)	China	22 (11/11)	1	Sepsis	85 mL/kg/h	Conventional therapy	Mortality
Quenot JP [17] (2015)	France	60 (31/29)	Multicenter	Sepsis	120 mL/kg/h	Conventional therapy	Mortality
Ronco C [8] (2000)	Italy+ USA	425 (279/146)	2	Acute renal failure	35 mL/kg/h	20 mL/kg/h	Mortality
Xia L [26] (2012)	China	60 (30/30)	1	Pancreatitis	220–250 ml/min	Conventional therapy	Mortality, MAP, HR, OI, APACHE II
Xie J [27] (2009)	China	41 (21/20)	1	ARDS	6 L/h	Conventional therapy	IL-6, OI, TNF, APACHE II
Zhang JC [28] (2013)	China	65 (37/28)	1	ARDS	45 mL/kg/h	Conventional therapy	Mortality, MAP, HR, OI

TBSA – total burn surface area; ARDS – acute respiratory distress syndrome; OI – oxygen index; TNF – tumor necrosis factor; IL-6 – Interleukin-6; MAP – mean arterial pressure; HR – heart rate; APACHE II – acute physiology and chronic health evaluation; CPFA – coupled plasma filtration adsorption.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bellomo R 2009	+	+	-	?	+	+	+
Bouman CS 2002	+	?	+	+	+	+	?
Boussekey N 2008	+	-	+	?	?	+	+
Bo You 2018	?	?	+	?	+	+	+
Chen X 2014	+	?	+	+	?	+	+
Chu LP 2012	?	?	+	+	?	+	+
Chung KK 2017	-	?	+	+	+	+	+
Combes A 2015	+	?	+	+	?	+	+
Ghani RA 2006	+	?	+	?	?	+	+
Guo J 2017	?	+	+	+	?	+	+
He WH 2016	+	?	-	+	+	+	+
Hu D2012	?	?	+	+	+	+	+
Jiang HL 2005	?	?	+	+	+	+	+
Joanne-Boyao O 2013	+	+	+	+	?	+	+
Liu C 2017	?	?	+	+	+	+	+
Peng Z 2010	?	?	-	+	+	+	+
Quenot JP 2015	?	+	-	+	+	+	+
Ronco C 2000	?	?	+	+	+	+	+
Xia L 2012	+	?	-	+	+	+	+
Xie J 2009	?	?	-	+	+	+	+
Zhang JC 2013	+	?	+	+	+	+	+

**Figure 2.** Results of methodological quality evaluation, 8 studies were regarded to be high risk bias for at least 1 high risk item, and the risk of bias was unclear for the remaining 13 studies.



**Figure 3.** The funnel plot of the publication bias analysis, this funnel plot is not visually symmetric and reveals potential publication bias. RR – relative risk; SE – standard error.

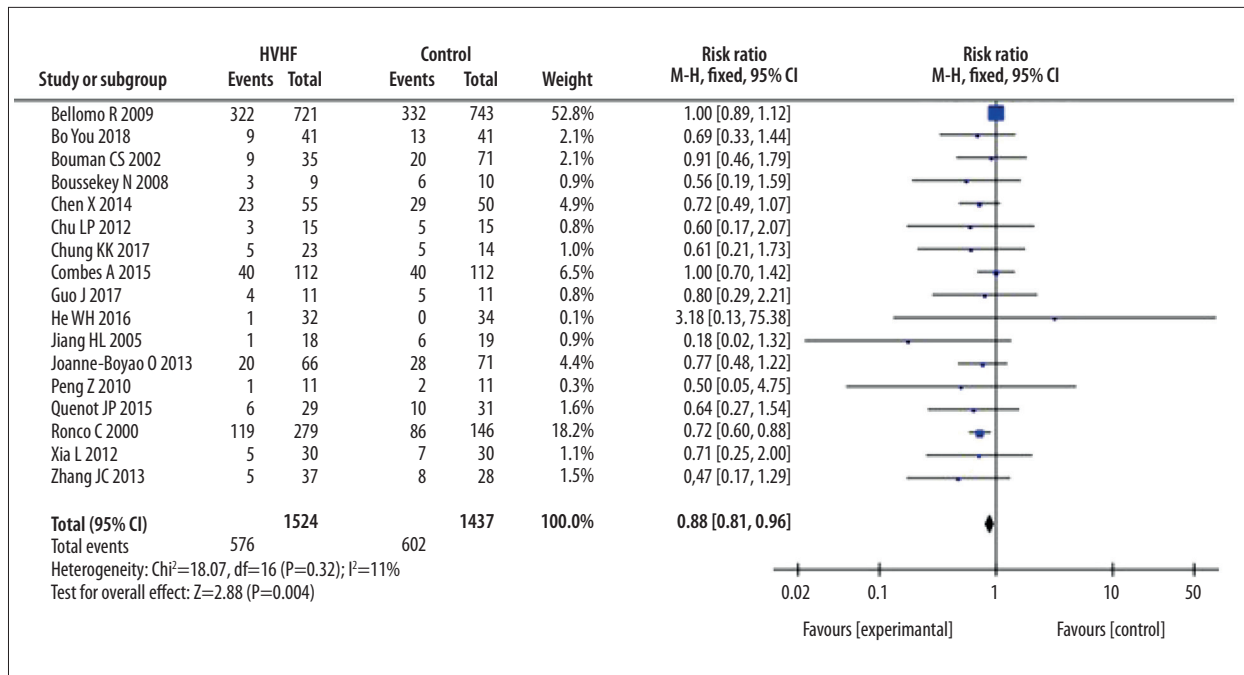
**Publication bias analysis**

In the meta-analysis of the impact of HVHF on the mortality of critically ill patients, a total of 17 studies [8,9,11,13, 15–19,21–24,26,28–30] were included, the number of studies was sufficient to conduct publication bias assessment; in the funnel plot, we chose RR value as the horizontal abscissa, while the SE (standard error) value as the ordinate, for the funnel plot was not symmetrical visually (Figure 3), we thought there was potential publication bias. In the evaluation of other outcomes, the number of studies included were all less than 10, and thus publication bias assessment was not performed, so it was unclear whether there was publication bias for the other outcomes.

**Results**

**Mortality**

The seventeen RCTs [8,9,11,13,15–19,21–24,26,28–30] included 1524 critically ill patients in the HVHF group and 1437 patients in the control group. Forest plot showed no statistical heterogeneity among studies ( $P=0.32$ ,  $I^2=11\%$ ), so the fixed effect model was used. The results showed that the mortality of the HVHF group was lower than that of the control group, the former mortality was 37.8% (576 out of 1524 patients), and the latter was 41.9% (602 out of 1437 patients). The difference was statistically significant ( $RR=0.88$ ,  $95\% CI=0.81$  to  $0.96$ ,  $P=0.004$ ) (Figure 4). Of the 17 studies, 7 studies reported patients who suffered from sepsis [8,13,15–17,19,21]. The Ronco et al. study [8] enrolled patients with AKI and found the mortality of AKI patients complicated with sepsis in their HVHF group was 69.7% (23 out of 33 patients) and in the control group it



**Figure 4.** Forest plot comparing mortality among HVHF group to that of control group. HVHF – high volume hemofiltration.

was 75% (15 out of 20 patients), thus, this study was classified as the Sepsis group in our subgroup analysis). Two studies included ARDS patients [9,28], 4 studies included SAP patients [22–24,26], 2 other studies included AKI patients [29,30], and the remaining 2 studies were respectively for severe burn patients [11] and postcardiac surgery shock patients [18]. Subgroup analysis of mortality based on different diseases demonstrated that HVHF reduced mortality in patients with sepsis and ARDS (RR=0.76, 95% CI=0.58 to 0.98,  $P=0.04$ ; RR=0.66, 95% CI=0.46 to 0.96,  $P=0.03$ ). However, there was no significant difference between HVHF and control groups in patients with SAP, AKI, or other diseases (RR=0.58, 95% CI=0.29 to 0.15,  $P=0.59$ ; RR=1.00, 95% CI=0.89 to 1.11,  $P=0.95$ ; RR=0.92, 95% CI=0.67 to 1.27,  $P=0.63$ ) (Figure 5).

### Inflammatory mediators

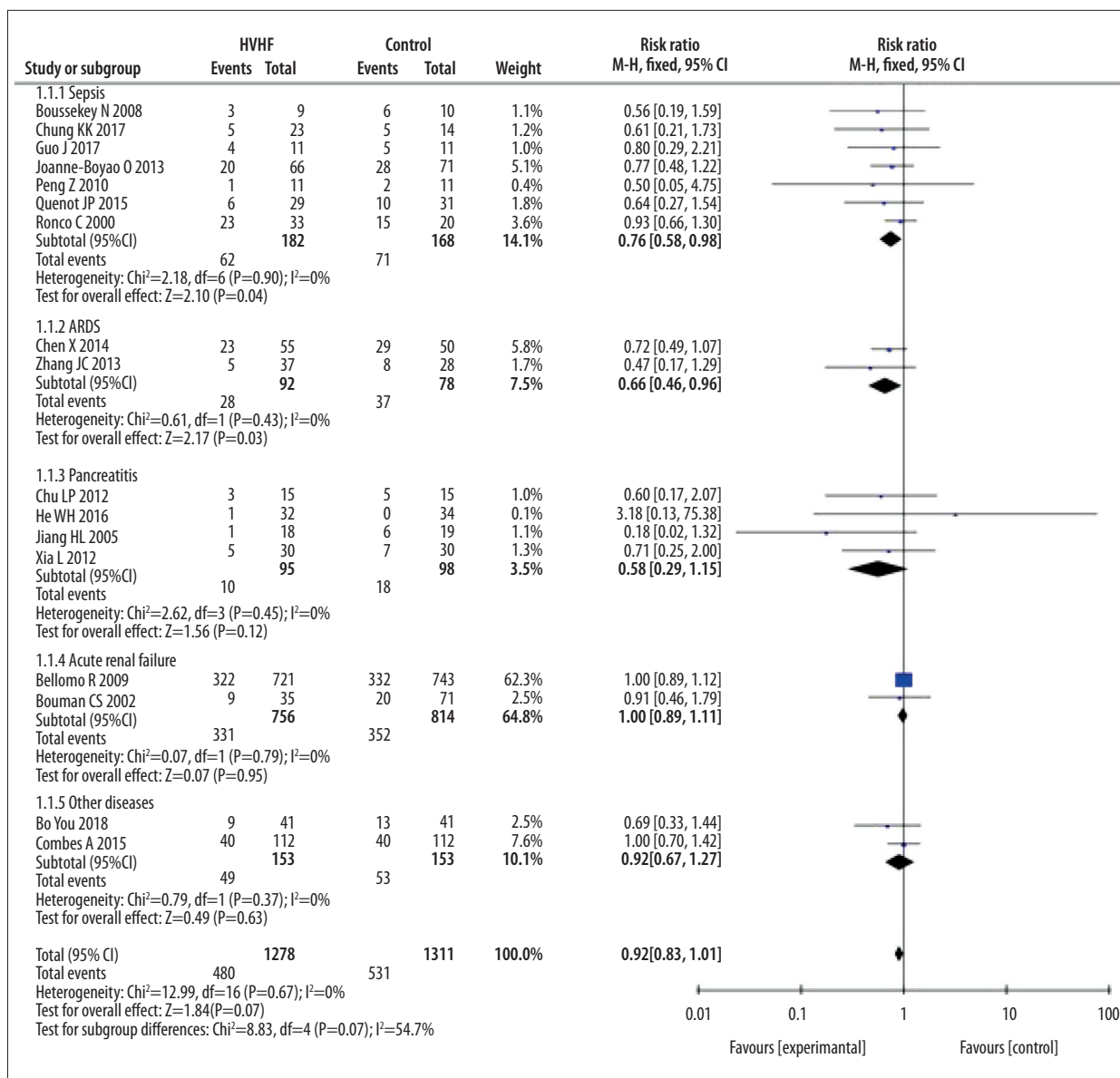
As for inflammatory mediators, the efficiency of HVHF to decrease the concentrations of plasma TNF and IL-6 levels were reported by 4 studies [9,20,25,27] (126 patients in HVHF group and 120 patients in control group) and 2 studies [19,25] (54 patients in HVHF group and 54 patients in control group) respectively; forest plots showed there was no statistical heterogeneity among the studies ( $P=0.28$ ,  $I^2=22%$ ;  $P=0.81$ ,  $I^2=0%$ ), so we used the fixed effect model for analysis. The results illustrated the levels of TNF and IL-6 in the HVHF group were lower than those in control group after treatment, and the differences were statistically significant (MD=-5.65, 95% CI=-8.21 to -3.10,  $P<0.0001$ ; MD=-5.31, 95% CI=-8.99 to -1.63,

$P=0.005$ ) (Figures 6, 7), which suggested HVHF could decrease the levels of plasma TNF and IL-6 in critically ill patients.

### Vital signs

In terms of HR there were 5 studies [14,20,22,26,28] (104 patients in the HVHF group and 98 patients in the control group) and in terms of MAP there were 3 studies [14,26,28] (82 patients in the HVHF group and 76 patients in the control group) included in our meta-analysis. There was no evident statistical heterogeneity among the studies for HR or MAP ( $P=0.75$ ,  $I^2=0$ ;  $P=0.48$ ,  $I^2=0$ ), thus we used the Peto Mantel-Haenszel fixed effect model. The results showed there were statistical differences for HR and MAP (MD=-8.18, 95% CI=-12.49 to -3.86,  $P=0.0002$ ; MD=5.21, 95% CI=0.33-10.1,  $P=0.04$ ), indicating the HVHF group had lower HR and higher MAP compared with the control group for these studies (Figures 8, 9).

For OI, there were 5 studies [9,20,26–28] included in the meta-analysis (150 patients in an HVHF group and 135 patients in a control group). There was large statistical heterogeneity among these studies as shown in the forest plot ( $P<0.00001$ ,  $I^2=100%$ ). The random effect model was used, and the results for OI showed there was no statistical difference between the 2 groups (MD=52.88, 95% CI=-49.64 to 155.39,  $P=0.31$ ) (Figure 10).



**Figure 5.** Forest plot of subgroup analysis comparing the mortality among HVHF group to that of control group based on different diseases. HVHF – high volume hemofiltration.

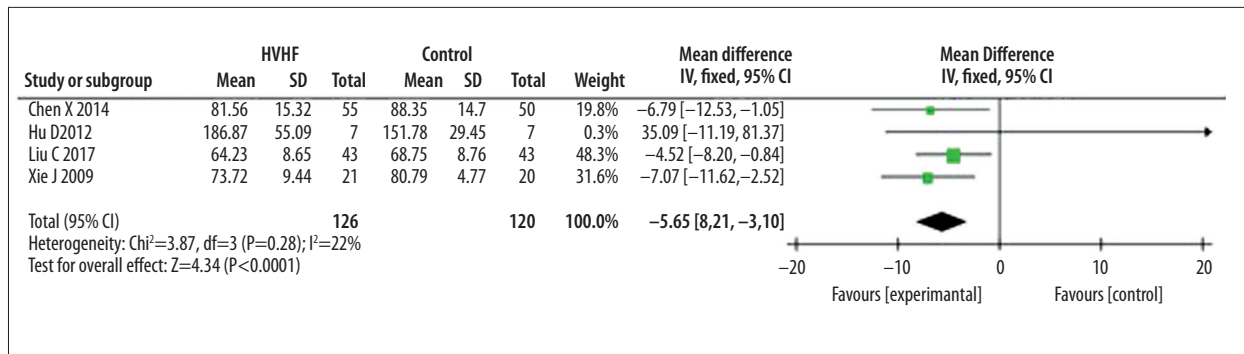
**APACHE II score**

For APACHE II score, 5 studies [20,22,23,26,27] were included with 105 patients in HVHF group and 106 in control group. We used the random effect model because of evident statistical heterogeneity ( $P < 0.0001$ ,  $I^2 = 90\%$ ). The pooled results showed no difference in APACHE II score between the 2 groups (MD = -0.93, 95% CI = -3.35 to 1.49,  $P = 0.45$ ) (Figure 11).

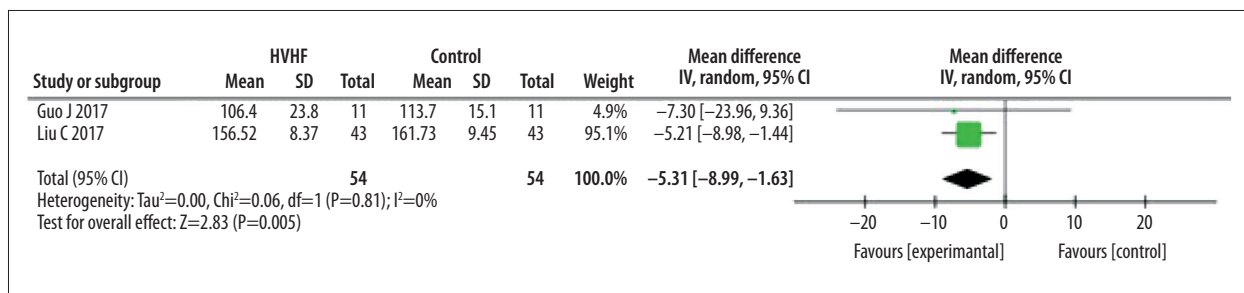
**Sensitivity analysis**

In order to test the robustness of our meta-analysis and find the potential sources of heterogeneity, we carried out

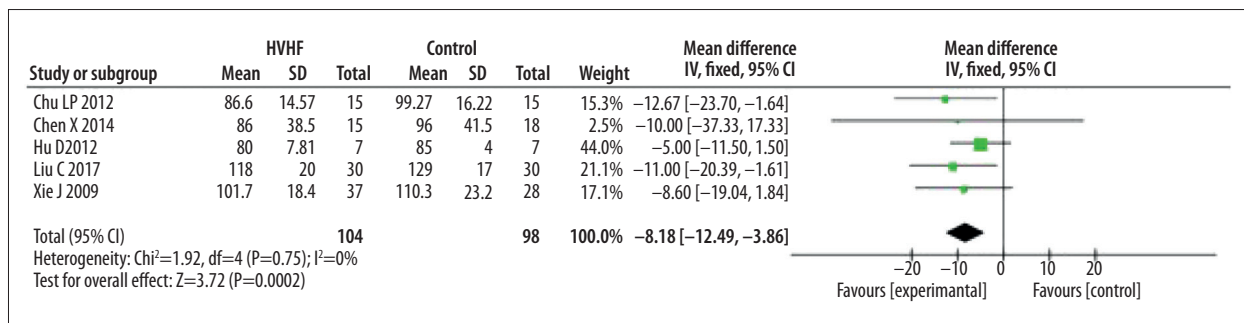
leave-one-out sensitivity analysis. The removal of any study could not change the results of mortality, plasma TNF, HR, OI or APACHE II score, which indicated the conclusions of these outcomes were sufficiently robust. In the sensitivity analysis of OI and APACHE II score, we found  $I^2$  failed to be less than 50% no matter what study was removed, which suggested the heterogeneity of those 2 meta-analyses didn't originate from a particular study, the heterogeneity might be related to the varied methodological quality among studies, different inter-fere measures in control group, or the difference in treatment duration. In the meta-analysis of IL-6, we found poor reliability for the result that showed no significant difference between the 2 groups when we removed the Liu et al. study [25];



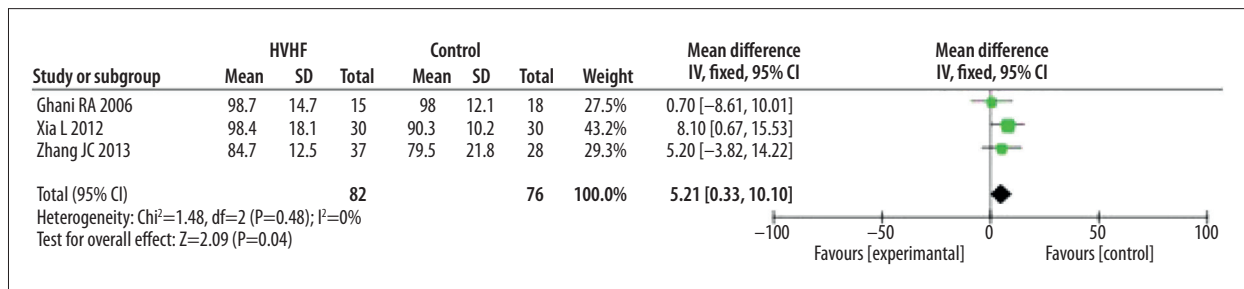
**Figure 6.** Forest plot comparing concentration of TNF among HVHF group to that of control group. TNF – tumor necrosis factor; HVHF – high volume hemofiltration.



**Figure 7.** Forest plot comparing concentration of IL-6 among HVHF group to that of control group. IL-6 – interleukin 6; HVHF – high volume hemofiltration.

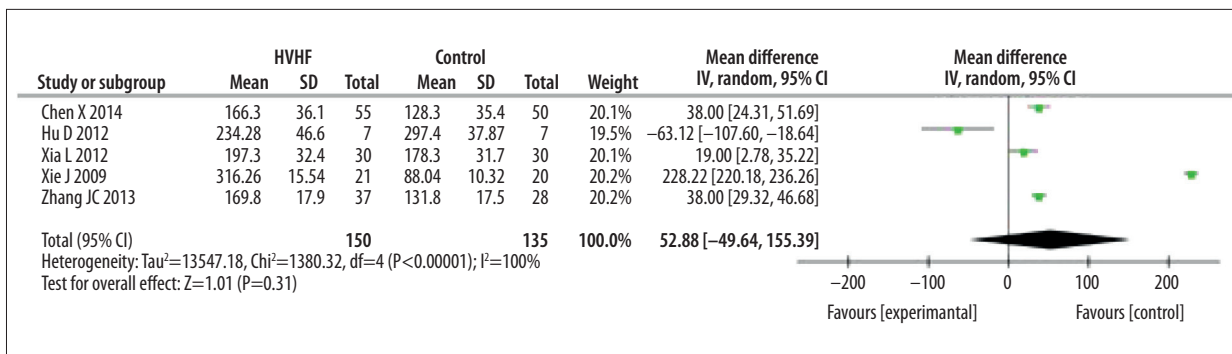


**Figure 8.** Forest plot comparing HR among HVHF group to that of control group. HR – heart rate; HVHF – high volume hemofiltration.

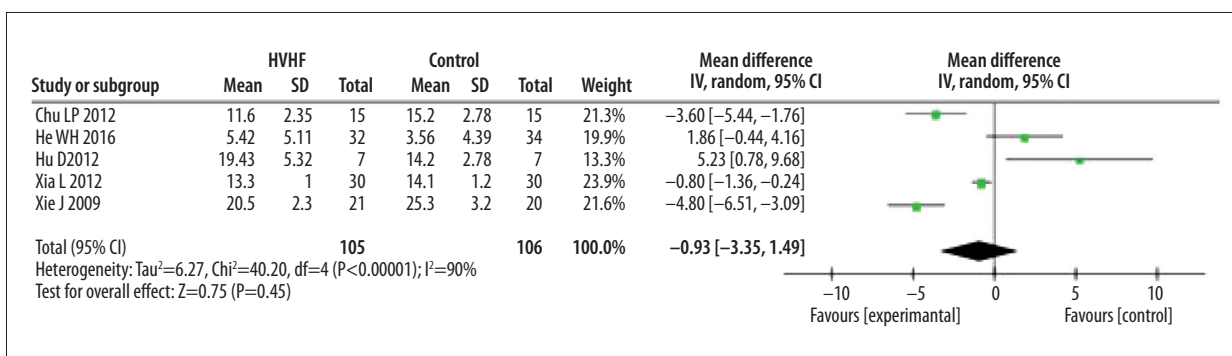


**Figure 9.** Forest plot comparing MAP among HVHF group to that of control group. MAP – mean arterial pressure; HVHF – high volume hemofiltration.





**Figure 10.** Forest plot comparing OI among HVHF group to that of control group. OI – oxygenation index; HVHF – high volume hemofiltration.



**Figure 11.** Forest plot comparing APACHE II score among HVHF group to that of control group. APACHE II – acute physiological and chronic health evaluation score; HVHF – high volume hemofiltration.

since only 2 studies were included, unreliable finding might be associated with the small number of studies. Similarly, in the analysis of MAP, the results reversed after removing the study of Xia et al. [26] or Zhang et al. [28], which suggested the conclusion was not robust. Therefore, caution should be exercised when reference to results of the effect of HVHF on IL-6 and MAP in critically ill patients.

## Discussion

Our meta-analysis included 21 RCTs (3135 critically ill patients). To the best of our knowledge, it is the largest meta-analysis that evaluated the clinical effect of HVHF on critically ill patients to date. This study demonstrated that HVHF was associated with the reduction of mortality of critically ill patients after the inclusion of several recently published RCTs, and the reliability of the conclusion was confirmed by sensitivity analysis. In the subgroup analysis, HVHF was found to effectively reduce mortality in patients with sepsis or ARDS, but no survival benefit was found in patients with SAP, AKI, or other diseases. As for the ability to eliminate the blood inflammatory mediators, our study revealed that HVHF could decrease the levels of TNF and IL-6 in critically ill patients. In terms of vital signs, this meta-analysis provided evidence that HVHF

decreased HR and increase MAP, but didn't show the advantage on OI compared to the control group. Similarly, the HVHF group didn't exhibit lower APACHE II score. Unfortunately, the effects of HVHF to remove IL-6 and increase MAP were overturned by sensitivity analysis.

Critical illnesses, such as sepsis [13,19], SAP [24–26], ARDS [9,27], severe burns [11,31] and even postcardiac surgery [18,32,33] might lead to systemic inflammatory response syndrome (SIRS). Under this condition, large amounts of inflammatory cells are activated, and those effector cells release various inflammatory mediators and cytokines, which are amplified by the “cascade effect” and even produce so-called “cytokine storms”. These excessive inflammatory mediators and cytokines not only cause disorder of the immune functions, but also damage the body directly through the injury of endothelial cells, thus leading to the occurrence of multiple organ dysfunction (MODS). Studies have shown in patients with severe trauma that the higher level of plasma inflammatory factors is associated with severer organ dysfunction and worse prognosis [34]. In the latter stage, a large number of anti-inflammatory factors such as IL-10 are released, which combined with the apoptosis of lymphocyte together lead to the immune paralysis and increase the chance of secondary infection [35]. How to inhibit the excessive release of inflammatory mediators to improve

the prognosis of critically ill patients has become a research hotspot in many countries today, TNF antagonists [36], interleukin-receptor antagonists [37] and other anti-cytokine drugs are emerging from time to time. However, no improvement in survival has been shown when using these drugs so far; the possible reason is that there is a complex network of inflammatory mediators in the state of systemic inflammation, and blocking a certain inflammatory mediator alone cannot fully reverse the state of systemic inflammation. HVHF can non-specifically eliminate water-soluble small and medium molecules (including most inflammatory mediators) in the blood, promoting the balance of pro-inflammatory and anti-inflammatory mediators by means of filtration, adsorption [38]. A meta-analysis of animal experiments conducted by Atan et al. [39] in 2013 indicated that HVHF had the potential to achieve appreciable IL-6 and IL-10 clearances. Our meta-analysis also came to a similar conclusion. In theory, HVHF alleviates systemic inflammation through removing large numbers of inflammatory mediators, and then improves prognosis of MODS caused by various critical illnesses. Just as Ronco et al. [40] once put forward, it's time to abandon the simple goal of achieving adequate renal support, the proper goal of CVVH in ICU should be multi-organ support therapy. In some clinical studies, although HVHF was effective in reversing shock and improving organ function, this effect didn't appear to be related to the removal of cytokines [16,41].

In addition to the benefits in maintaining a balance of water and electrolytes, Honore et al. [42] also proposed the following hypothesis: when removal is occurring on the blood compartment side, the inflammatory mediators in the tissue side enter the blood for the concentration difference, which leads to the level of mediators in the blood not decreasing significantly, while the mediators in the tissue fluid decrease effectively, therefore, no further harm can be done to the tissue. Our meta-analysis showed that HVHF reduced mortality in patients with sepsis and ARDS, but not in patients with SAP, AKI, or other diseases. In addition, it had no substantial influence on OI, or APACHE II score. The reasons might be as follows: on the one hand, the pathogenesis of different diseases is not entirely the same, the efficacy of HVHF for different illnesses is quite different. On the other hand, excessive loss of electrolytes, micronutrients, vitamins or drugs (e.g., antibiotics) when removing the inflammatory mediators cannot be ignored [43], which will have negative impact on the prognosis of patients.

In recent years, as the efficacy of HVHF has been controversial, meta-analysis about HVHF emerged from time to time, but mainly focused on septic patients. In 2010, Liu et al. [44] included 9 studies (only 3 RCTs) in their meta-analysis of HVHF in septic patients. They concluded that HVHF could effectively reduce mortality of sepsis (OR=0.33, 95% CI=0.17 to 0.64,  $P<0.01$ ). However, in 2014, Clark et al. [45] updated their

meta-analysis and showed there was little evidence to recommend HVHF in sepsis patients (OR=0.76, 95% CI, 0.45 to 1.29,  $P>0.05$ ); they added only 4 RCTs. In 2017, a meta-analysis conducted by Borthwick et al. [45] also came to a similar conclusion to that of Clark et al. [43], considering the small number of studies with only 201 participants were included, and that this could affect the reliability of outcomes, the authors argued that researchers should consider additional RCTs that are large and multi-centered and have clinically relevant outcome measures [45]. Besides, in a study of critically ill patients, a meta-analysis published in 2014 detected no clear overall beneficial effect of HVHF compared to standard volume hemofiltration [46], while the meta-analysis recently published by Luo et al. [47] demonstrated that HVHF significantly reduced the incidence of 28-day mortality. Although our findings about mortality were similar to the Luo et al. study, a strength of our analysis was that we first performed subgroup analysis for mortality based on different diseases. Our study is also the first meta-analysis that has assessed the effect of HVHF on patients with SAP and ARDS. We also included several additional studies that were not included in the prior meta-analyses. In general, the conclusions of the meta-analyses published in recent years on HVHF have not been consistent, and most of the analyses included only a small number of studies. With the new publication of several RCTs in recent years, more high-level evidence-based medical research was expected to evaluate the value of HVHF for critically ill patients. After strict screening, and including the newly published RCTs, especially those published in the last 2 years, our meta-analysis concluded that HVHF might reduce the mortality of critically ill patients.

However, this meta-analysis also has some limitations: First, most of the studies included were not double-blinded and this might cause bias. Second, in terms of mortality, there were 14 studies that looked at 28-day mortality, and the remaining 3 studies used different observation times (90-day mortality, 15-day mortality, and hospitalized mortality). Third, there is still a lack of consistency on the dose of HVHF applied internationally; the dose of HVHF ranged from 35 mL/kg/hour to 120 mL/kg/hour in our meta-analysis HVHF group. These limitations might impact outcomes; therefore, we still need to be cautious when referencing to the results of this study and we must take the actual situation of the patients into consideration.

## Conclusions

Our meta-analysis of published RCTs found that HVHF showed some ability regarding removing plasma inflammatory mediators (TNF and IL-6), improving circulation state (lower HR and higher MAP), and reducing mortality of critically ill patients, but it had no substantial influence on OI or APACHE II score.

However, for most RCTs included in our meta-analysis, the quality was not high, and the poor reliability of findings for IL-6 and MAP, suggest the need to conduct RCTs with higher quality to further clarify the clinical effects of HVHF in the treatment of critically ill patients in the future.

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## Conflict of interest

None.

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