BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014171
Article Type:	Research
Date Submitted by the Author:	06-Sep-2016
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Urology
Keywords:	acute kidney injury, dose, intensive care unit

Delivered dose of continuous renal replacement therapy in acute kidney injury of patients in the intensive care unit: an updated systematic review and meta-analysis

Running title: Renal replacement therapy in acute kidney injury

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Word count: 3482

ABSTRACT

Objective: The purpose of this study was to conduct a systematic review and meta-analysis to determine the effect of intensity (delivered dose) of continuous renal replacement therapy on the survival of patients and acute renal failure.

Design: Meta-analysis.

Setting: Included studies were randomized controlled trials, two-arm prospective or retrospective studies.

Participants: Critically ill patients with acute kidney injury.

Interventions: Continuous renal-replacement therapy.

Primary and secondary outcome measures: The major outcomes of death up to 90-days (90 day mortality), Intensive Care Unit (ICU) mortality, hospital mortality, and length of hospital or ICU stay

Result: Eight studies were included in the analysis for a total of 2970 patients. For the primary outcomes, patients treated with high-dose continuous renal replacement therapy did not have a higher risk of death than those with low- or standard-dose renal-replacement therapy. There was also no significant difference between the high- or low-intensity renal replacement therapy groups in terms of length of ICU or hospital stay. Sensitivity analysis and quality assessment indicated the findings are robust.

Conclusion: The study found no survival benefit of high-intensity compared with low- or standard- intensity continuous renal replacement therapy in critically ill patients with acute kidney injury.

Keywords: acute kidney injury, dose, intensive care unit, intensity, renal dialysis, renal-replacement therapy

Strengths and limitations of this study

- The strength of our analysis is the meta-regression analysis with evaluated the impact of patients with sepsis or septic shock on the overall pooled analysis.
- The limitation of our analysis is the considerable variation across the studies with regard to the prescribed doses for the high-, less- intensive CRRT.

INTRODUCTION

Acute kidney injury (AKI) occurs in at least 5% of patients with who are admitted to the intensive care unit (ICU) and is an independent predictor of mortality.[1-3] In addition, about 50% of patients with septic shock will experience AKI.[4] The prognosis of patients with AKI is low with a mortality rate of up to 70% despite improvements in hemodialysis methodology and availability.[5-7]

Two methods for obtaining clearance in patients with AKI who require renal support are hemofiltration and hemodialysis. Hemofiltration uses convection to aid in the removal of both high and low molecular weight solutes, which is determined by the pore size of the membrane.[8] Hemodialysis removes solute by diffusion out of the bloodstream into the [8] dialysate using a concentration gradient, and removes low molecular weight molecules. Hemodialysis has limited ability to clear high molecular weight substances. The ability of hemofiltration to remove both large and small molecules, which may include toxic mediators of sepsis and inflammation, is thought to be the reason for the superiority of hemofiltration compared with hemodialysis.[8]

A significant percentage of patients with AKI require renal replacement therapy (RRT).[2] For patients who require RRT, the treatment dose or intensity may influence outcomes. Continuous renal replacement therapy (CRRT) is an option for treating patients with AKI and may provide better clearance for toxic molecules, acid-base

homeostasis, and removal of inflammatory mediators that can contribute to organ injury and dysfunction.[9-13] However, the optimum dosage of CRRT, including the ideal timing and intensity is not clear. Some clinical studies have found benefits for intensive doses of CRRT in mortality,[14,15] while other have not.[16-19]

Several prior systematic reviews and meta-analyses have assessed the use of CRRT for treating AKI. These studies found that high-dose CRRT was not associated with a decrease in mortality in patients with AKI.[20-22] Since the publication of these reviews, additional clinical studies have been published that addressed the use of CRRT in AKI.[23,24] Hence, we conducted an updated systematic review and meta-analysis to evaluate the effect of intensity (delivered dose) of CRRT on the survival of patients with AKI in an ICU setting. This study focuses on patients receiving hemofiltration.

MATERIAL AND METHODS

Search strategy

This meta-analysis was performed according to the PRISMA guidelines. PubMed, Medline, Cochrane, Google Scholar databases were searched until June 22, 2016 using the following search terms: renal-replacement therapy, renal dialysis, acute kidney injury, intensive care unit, intensity, dose. Included studies were randomized controlled trials,

two-arm prospective, retrospective, or cohort studies that evaluated critically ill patients with acute kidney injury who received CRRT. Included studies had to report quantitative outcomes of interest. Letters, comments, editorials, case report, proceeding, and personal communications were excluded. Studies that evaluated patients who had received previous renal replacement therapy during the same hospital admission or who were on maintenance dialysis for end-stage kidney disease were excluded. Two independent reviewers reviewed all potential studies, and a third reviewer was consulted to resolve any discrepancies.

Data extraction and quality assessment

The following information/ data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and the major outcomes of death up to 90-days (90 day mortality), Intensive Care Unit (ICU) mortality, hospital mortality, and length of hospital or ICU stay.

The quality of the included studies was evaluated using the Cochran Q and the I^2 statistic.[25]

Statistical analysis

Primary outcomes were 90-day mortality, ICU mortality, and hospital mortality. Secondary outcomes were length of ICU and hospital stay. Comparisons of mortality rate between patients receiving high- or low-intensity CRRT were presented by odds ratio (OR) and 95% confidence interval (95% CI); an OR > 1 indicated that patient treated with high intensity CRRT had higher risk of death. The effect size of length of ICU and hospital stay was reported as difference in means; difference in means > 0 indicated longer ICU or hospital stay in patients treated with high intensity CRRT. Pooled estimates for odds ratios and difference in means were calculated by DerSimonian and Laird random-effects model. A 2-sided P-value < 0.05 was considered statistically significant.

Heterogeneity was assessed using the Cochran Q and the I^2 statistic. For the Q statistic, P <0.10 was considered statistically significant for heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity. The suggested ranges are as follows: no heterogeneity (I^2 = 0% to 25%), moderate heterogeneity (I^2 =25% to 50%), large heterogeneity (I^2 = 50% to 75%), and extreme heterogeneity (I^2 = 75% to 100%).

Sensitivity analysis was performed for the primary outcomes using the leave-one-out approach. Due to incongruous definition of grouping based on the treatment dose of CRRT, additional sensitivity analysis was performed to examine the stability of pooled estimates according to various cut-off points of prescribed dose. Meta-regression analysis

was performed to examine whether the percentage of patients with sepsis or septic shock influenced the pooled estimates of association between CRRT and outcomes of interest. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

A total of 363 studies were identified in the initial search of which 246 were excluded for being duplicate publications (Figure 1). Of the remaining 117 studies, 100 were excluded for not being relevant, and nine more were excluded for not reporting outcomes of interest, being a duplicate with an included study, or administered intermittent or low doses of CRRT.

Eight studies were included in the meta-analysis.[14,16,17,19,23,24,26,27] Seven were randomized controlled trials [14,16,17,23,24,26] and one was a prospective study [27] (Table 1). A total of 2970 patients were included, and the number of patients per study ranged from 19 to 1465. The mean age ranged from 59 to 73 years, most of the patients were male (54% to 80%) and the causes for requiring acute kidney injury were sepsis, surgery (including cardiovascular surgery), and septic shock. The type of treatment and the definition of high-dose or more-intensive therapy varied across the

studies. The doses used also were heterogeneous among the studies, ranging from 20 to 85 mL/kg/h.

Meta-analysis

For analysis of the primary outcomes of within 90-day morality,[14,17,23,24] ICU mortality,[16,17,19,27] and hospital mortality [16,17,19,24], there was low to moderate heterogeneity across the studies for each outcome (Q = 4.10, P = 0.251, I^2 = 26.7%; Q = 2.24, P = 0.524, I^2 = 0%; and Q = 1.49, P = 0.686, I^2 = 0%, respectively). The pooled results showed no significant difference in the 90-mortality rate between patients treated with high-volume or more intensive CRRT and those that were not (pooled OR = 0.899, 95% CI = 0.728 to 1.109, P = 0.319) (Figure 2A). The findings were similar for ICU (pooled OR = 1.120, 95% CI = 0.939 to 1.335, P = 0.209) and hospital mortality (pooled OR = 1.025, 95% CI = 0.809 to 1.297, P = 0.839) (Figure 2B and 2C).

Large heterogeneity was observed across the seven studies that reported data for length of hospital stay (Q=25.10, P = 0.002, I^2 = 76.1%). No heterogeneity was observed for data regarding length of hospital stay (Q=1.74, P=0.784, I^2=0%). No significant difference was found in the length of ICU between treatment groups (pooled difference in means = -2.092, 95% CI = -5.638 to 1.453, P = 0.247) (Figure 3A). The results were

similar for length of hospital stay (pooled difference in means = -0.034, 95% CI = -2.382 to 2.313, P = 0.977) (Figure 3B).

Sensitivity analysis, meta-regression analysis, and quality assessment

Sensitivity analysis using the leave-one-out approach showed that the pooled results for the 3 primary outcomes did not significantly change when each study was left out in turn. (Figure 4). Furthermore, use of various cut-off points of prescribed dose to identify treatment intensity had no significant impact on the results (Table 2). These findings indicate that the findings are not overly influences by any one study or different dose cut-off points, and suggest the findings are robust.

We used meta-regression analysis on the population of patients with sepsis or septic shock to evaluate whether these two population affect the overall pooled analysis. The reason for the analysis was based on the fact that sepsis and septic shock differ in terms of emergent setting and presence of systemic infection. The results of meta-regression analysis showed that the regression coefficients had a slope close to 0, indicating that the associations between CRRT and selected outcomes were not influenced by the percentage of patients with sepsis or septic shock (all P-values for all slope coefficients >0.05) (Table 3).

Assessment of the quality of the included studies, using Cochrane's collaboration tool, indicated that there was low risk of bias for most of the studies (Figure 5A and 5B). One exception was the study of Vesconi et al. [27] which showed a high risk of selection, performance, and detection bias (Figure 5B). Overall, the included studies were of adequate quality.

DISCUSSION

The purpose of this study was to conduct a systematic review and meta-analysis to provide an update meta-analysis on the proper dosage of CRRT and the effect of dose on mortality, length of hospital stay or stay in the ICU in patients with AKI.. Eight studies were included in the analysis for a total of 2970 patients. For the primary outcomes, patients treated with high-intensity CRRT did not have higher risk of death than those with low dose renal-replacement therapy. There was also no significant difference between the high- or low-intensity CRRT groups in terms of length of ICU or hospital stay. Sensitivity analysis and quality assessment indicated no one study dominated the findings and that the included data was of adequate quality.

The study updates the analysis of the impact of high- versus low- intensity CRRT on survival and hospital/ICU stay in critically ill patients with AKI, and is consistent with

the results of three prior meta-analyses, all of which found no survival benefit of high intensity CRRT in patients with acute renal failure.[20-22] Although, our findings are similar to prior studies, a strength of our analysis is the meta-regression analysis with evaluated the impact of patients with sepsis or septic shock on the overall pooled analysis. The meta-regression analysis indicated that heterogeneity due to a mixed population of sepsis and septic shock patients did not influenced the pooled results. In addition, we included two additional studies that updated the analysis compared with prior meta-analyses. The consistency of finding across the different meta-analyses and findings of our meta-regression analysis suggest that the delivered dose is not affected by the presence of systemic infection; and any variance seen when treating patients may reflect the severity of the acute kidney disease and/or an individual patient's condition.

The data from clinical studies on the benefit of high intensity CRRT in critically ill patients have been inconsistent. Ronco et al (2000) found improved survival associated with higher total effluent volumes (>45 mL/kg/h) in patients with septic AKI [14] and Boussekey et al (2008), in a small pilot study, found high intensity CRRT was associated with improved hemodynamic profile.[26] However, Boussekey et al did not find any significant effect on survival or organ dysfunction. In contrast, two randomized controlled multicenter studies found no added survival benefit of high intensity compared with standard intensity CRRT in critically ill patients with AKI.[17,18] A more recent

study by Joannes-Boyau et al also found no evidence that high-intensity (70 mL/kg/h) compared with standard-intensity (35 ml/kg/h) CRRT resulted in reduction in 28-day mortality or to early improvements in hemodynamic profile or organ dysfunction in septic shock patients with AKI.[23] The authors conclude that high-intensity CRRT as used in their study cannot be recommended for treatment of septic shock complicated by AKI.[23]

A prior meta-analysis compared the efficacy of extended daily dialysis (EDD) and CCRT in treating patients with acute kidney injury.[28] Zhang et al (2015) included 17 studies from 2000-2014 with a total of 1208 patients. Meta-analysis of the included RCTs (n=10) found no difference in mortality rates between EDD and CRRT (relative risk, 0.90; 95% CI, 0.74-1.11; P=0.3). However, lower mortality risk was observed with EDD compared with CRRT in observational studies (relative risk, 0.86; 95% CI, 0.74-1.00; P=0.05). For both RCTs and observational studies recovery of kidney function, fluid removal, and days in the ICU were similar between procedures. The authors conclude that the findings from RCTs suggest that CRRT and EDD have similar efficacy, and that the difference in mortality observed in analysis of the observational studies may be confounded by selection bias. The potential confounding effect of observational studies is also indicated by our findings from our quality assessment of the included studies as the

study of Vesconi et al. [27] had a high risk of selection bias, as well as, performance and detection bias.

Our study was limited by the considerable variation across the studies with regard to the prescribed doses for the high-, less- intensive CRRT. It is difficult to standardize the prescribed and delivered doses across the studies due to differences in equipment used and personnel. There was also a wide range of effect size and several of the studies reported opposite findings. In addition, only four of the included studies reported data for the primary endpoint of mortality within 90-days, and not all the studies were randomized controlled trials. In addition, due to the heterogeneity of dosing across studies and the differences in the definition of high-dose or more-intensive dose, and the fact the raw data for each group was not presented, it was difficult to group the analysis according to a cut-off value of the standard of care does of 35 mL/kg/hr. For example, Vesconi et al. defined 35mL/kg/hr as “more intensive” and compared the finding of that dosing with “less intensive” <20 to 34 mL/kg/hr. This type of definition differs from that of Zhang et al. which compared 85 mL/kg/hr with 50 mL/kg/hr. It is highly possible that this variability may have confounded our results. However, sensitivity analysis found that no one study overly influences the findings; hence suggesting that although heterogeneity in dosing exists, the pooled results are robust. Larger numbers of randomized controlled studies with more consistent dosing are required to further explore the use of high-

intensity CRRT in treating critically ill patients with AKI. Investigation of the cost-effectiveness of the high- and low-intensity CRRT is also warranted.

This meta-analysis did not find a survival benefit of high-intensity CRRT compared with low-intensity CRRT in patients with AKI. It also did not find an association of high-intensity CRRT with reduced ICU or hospital stay. However, additional well-designed studies are necessary to further investigate what is the optimal CRRT for critically ill patients with AKI.

Acknowledgements

We would like to express our sincere gratitude to our colleagues whose name did not appear on the paper but also contributed to the article. We especially thank Xiao Tan, Jifu Jin and Zhouping Zou for collecting the data.

Funding source

Key Project in the National Science & Technology Pillar Program in the Twelfth Five-year Plan Period (2011BAI10B07); Scientific Research Project of Shanghai Committee of Science and Technology (12DJ1400201).

Competing interests: None

Author's contribution:

PL: study design, literature research, manuscript preparation; LPQ: study design, literature research, manuscript preparation; DQ: manuscript preparation, data acquisition, data analysis; BS: manuscript preparation, data acquisition, data analysis; YW: manuscript preparation, data acquisition, data analysis; JRX: manuscript preparation, data acquisition, data analysis; WHJ: data analysis, statistical analysis; HZ: data analysis, statistical analysis; XQD: guarantor of integrity of the entire study, study concepts; JT: study concepts, study design, guarantor of integrity of the entire, study, manuscript editing

Ethics approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent: Not applicable

Data sharing statement: No additional data available

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram

Figure 2. Meta-analysis for treatment effect of continuous renal replacement therapy on mortality (A) within 90 days, (B) in ICU and (C) in hospital

Figure 3. Meta-analysis for treatment effect of continuous renal replacement therapy on (A) ICU stay and (B) hospital stay.

Figure 4. Sensitivity analysis using leave-one-out approach for treatment effect of continuous renal replacement therapy on mortality (A) within 90 days, (B) in ICU and (C) in hospital.

Figure 5. Quality assessment.

Table 1. Summary of basic characteristics of included studies for meta-analysis

Study	Study design	No of patients	Treatment dose	Prescribed dose (mL/kg/h)	Delivered Dose (mL/kg/h)*	Duration (days)*	Age (yrs)*	Male (%)	Major cause of AKI	Sepsis	Oliguria
Joannes-Boyau (2013)	RCT	66	High-volume HF	70	65.6 (40–67.9)*	96 hrs	68 (58–77)*	68.0%	Sepsis	66 (100%)	
		71	Standard-volume HF	35	33.2 (28.7–33.6)*		70 (58–75)*	54.0%		71 (100%)	
Vesconi (2009)	Prospective	75	More-intensive	35	44.8 (9.4)	2 (1, 3)*	61.01 (17.4)	58.1%		33 (40.5%)	36 (48.6%)
		202	Less-intensive	21-34	26.9 (4.0)	4 (2, 8)*	63.48 (15.9)	67.8%	Surgery	81 (40.1%)	84 (41.7%)
		61	Less-intensive	20	15.4 (4.2)	3 (2, 6)*	59.05 (19.0)	73.8%		19 (31.2%)	30 (49.5%)
Zhang (2012)	RCT	141	EHVHF	85	87.54 (12.54)	9.38 (12. 06)	56.62 (16.38)	58.9%	Septic shock	72 (51.06%)	
		139	HVHF	50	49.99 (9.65)	8.88 (10.79)	59.96 (18.81)	64.0%		69 (49.64%)	
Bouman (2002)	RCT	35	EHV	72	48.2 (42.3–58.7)*	68.5 (28.0–140.8)*, †	68 (13)	60.0%			35 (100%)
		35	ELV	24-36	20.1 (17.5–22.0)*	94.0 (53.0–181.5)*, †	70 (10)	57.0%	Cardiosurgy		35 (100%)
		36	LLV	24-36	19.0 (16.6–21.2)*	69.5 (28.3–157.7)*,†	67 (13)	61.0%			30 (100%)
Tolwani (2008)	RCT	100	High Dosage	35	29	10.0 (9.8)	58 (16)	59.0%	Septic shock	54 (54%)	64 (64%)
		100	Standard Dosage	20	17	9.7 (11.3)	62 (15)	57.0%		54 (54%)	63 (63%)
Bellomo (2009)	RCT	722	Higher-Intensity CRRT	40	33.4 (12.8)	6.3 (8.7)	64.7(14.5)	65.7%	Sepsis	360 (49.9)	430 (59.6%)
		743	Lower-Intensity CRRT	25	22 (17.8)	5.9 (7.7)	64.4 (15.3)	63.5%		363 (48.9)	444 (59.8%)
Boussekey (2008)	RCT	9	HVHF	65	62	7 (2–17)*	68 (58–74)*	78.0%	Sepsis	9 (100 %)	
		10	LVHF	35	32	6 (2–14)*	72.5 (54–77)*	80.0%		10 (100%)	
Ronco (2000)	RCT	146		20			61 (10)	55.5%		20 (14%)	
		139		35			59 (9)	55.4%	Surgery	17 (12%)	
		140		45			63 (12)	57.1%		15 (11%)	

CRRT, continuous renal-replacement therapy; EHV, early high-volume hemofiltration; EHVHF, extra high-volume hemofiltration; ELV, early low-volume hemofiltration; HVHF, high-volume hemofiltration; LLV, late low-volume hemofiltration LVHF, low-volume hemofiltration; RCT, randomized controlled trials,

Table 2. Sensitivity-analysis for treatment effect on mortality according to different cut-off point for prescribed dose

	Number of studies included	Pooled odds ratio	Lower limit	Upper limit	Z-Value	P-Value
(A) Mortality within 90 days						
50 mL/kg/h	2	0.969	0.655	1.434	-0.156	0.876
40 mL/kg/h	3	0.831	0.500	1.382	-0.712	0.476
30 mL/kg/h	2	0.729	0.385	1.381	-0.970	0.332
(B) ICU mortality						
40 mL/kg/h	2	1.039	0.845	1.278	0.365	0.715
30 mL/kg/h	3	1.129	0.922	1.382	1.175	0.240
(C) Hospital mortality						
50 mL/kg/h	2	1.112	0.751	1.647	0.532	0.595
40 mL/kg/h	2	1.015	0.709	1.453	0.080	0.936
30 mL/kg/h	2	0.978	0.728	1.314	-0.145	0.884

Table 3. Meta-regression analysis for each outcome

Outcomes	Intercept[a]	Slope[a]
Mortality within 90 days	-0.416 (0.191)	0.007 (0.004)
ICU mortality	0.306 (0.346)	-0.004 (0.007)
Hospital mortality	0.305 (0.344)	-0.006 (0.007)
Length of ICU stay	-2.889 (1.901)	0.030 (0.038)
Length of hospital stay	-1.739 (4.133)	0.035 (0.081)

[a]Presented as point estimate of coefficient and standard error.

Figure 1

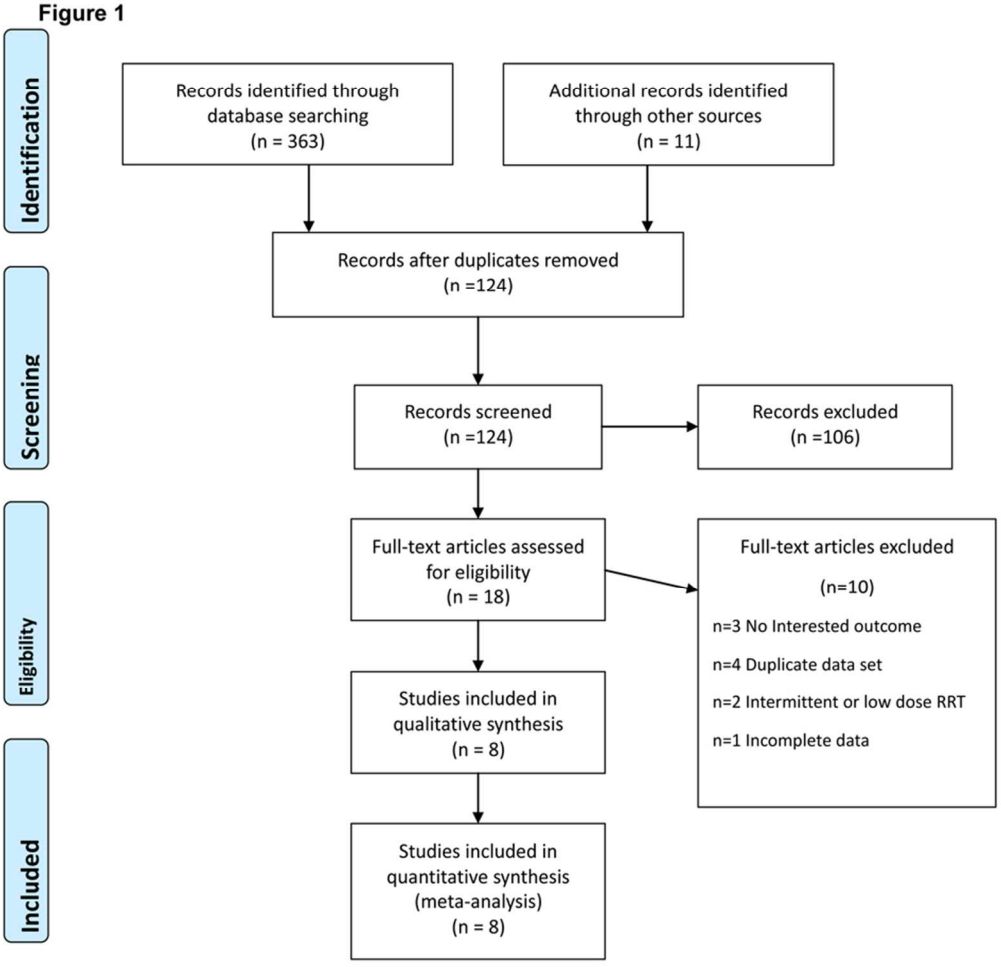
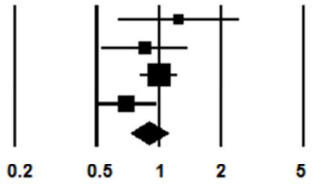


Figure 1

80x79mm (300 x 300 DPI)

(A) 90-day mortality

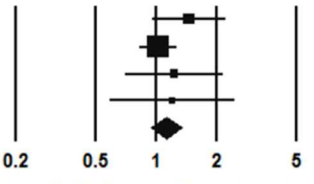
Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	1.240	0.633	2.431	0.628	0.530
Zhang (2012)	0.854	0.528	1.383	-0.642	0.521
Bellomo (2009)	0.997	0.811	1.225	-0.033	0.974
Ronco (2000)	0.696	0.498	0.972	-2.125	0.034
Pooled	0.899	0.728	1.109	-0.996	0.319



Heterogeneity test: Q = 4.10, P = 0.251, I^2 = 26.7%

(B) ICU mortality

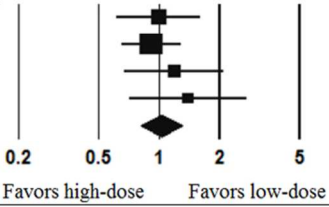
Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Vesconi (2009)	1.456	0.953	2.225	1.735	0.083
Bellomo (2009)	1.026	0.827	1.273	0.233	0.816
Tolwani (2008)	1.227	0.700	2.152	0.715	0.475
Bouman (2002)	1.199	0.584	2.465	0.495	0.621
Pooled	1.120	0.939	1.335	1.257	0.209



Heterogeneity test: Q = 2.24, P = 0.524, I^2 = 0%

(C) Hospital mortality

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhang (2012)	0.993	0.613	1.608	-0.029	0.977
Bellomo (2009)	0.913	0.647	1.288	-0.521	0.602
Tolwani (2008)	1.185	0.669	2.099	0.583	0.560
Bouman (2002)	1.391	0.707	2.735	0.957	0.339
Pooled	1.025	0.809	1.297	0.203	0.839



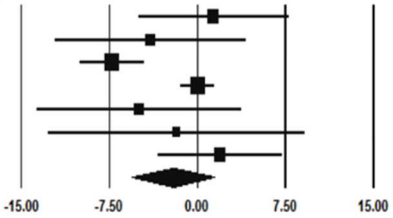
Heterogeneity test: Q = 1.49, P = 0.686, I^2 = 0%

Figure 2

80x94mm (300 x 300 DPI)

(A) Length of ICU stay

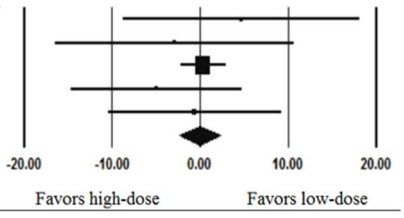
Study name	Statistics for each study				
	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	1.330	-5.076	7.736	0.407	0.684
Zhang (2012)	-4.010	-12.141	4.121	-0.967	0.334
Vesconi (2009)	-7.300	-10.003	-4.596	-5.292	0.000
Bellomo (2009)	0.000	-1.449	1.449	0.000	1.000
Tolwani (2008)	-5.000	-13.704	3.704	-1.126	0.260
Boussekey (2008)	-1.840	-12.765	9.085	-0.330	0.741
Bouman (2002)	1.910	-3.417	7.236	0.703	0.482
Pooled	-2.092	-5.638	1.453	-1.157	0.247



Heterogeneity test: Q = 25.10, P < 0.001, I^2 = 76.1%

(B) Length of hospital stay

Study name	Statistics for each study				
	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	4.630	-8.836	18.096	0.674	0.500
Zhang (2012)	-2.940	-16.517	10.637	-0.424	0.671
Bellomo (2009)	0.300	-2.286	2.886	0.227	0.820
Tolwani (2008)	-5.000	-14.644	4.644	-1.016	0.310
Bouman (2002)	-0.673	-10.525	9.178	-0.134	0.893
Pooled	-0.034	-2.382	2.313	-0.029	0.977



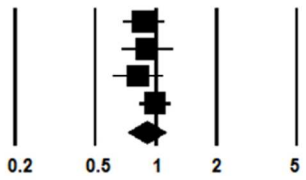
Heterogeneity test: Q = 1.74, P = 0.784, I^2 = 0%

Figure 3

80x64mm (300 x 300 DPI)

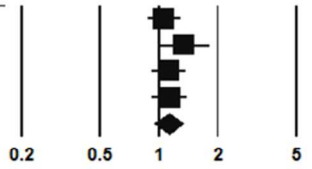
(A) 90-day mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Joannes-Boyau (2013)	0.867	0.686	1.096	-1.195	0.232	
Zhang (2012)	0.906	0.679	1.209	-0.672	0.502	
Bellomo (2009)	0.815	0.612	1.085	-1.403	0.161	
Ronco (2000)	0.991	0.825	1.189	-0.102	0.919	
Pooled	0.899	0.728	1.109	-0.996	0.319	



(B) ICU mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Vesconi (2009)	1.060	0.873	1.287	0.589	0.556	
Bellomo (2009)	1.336	0.984	1.815	1.854	0.064	
Tolwani (2008)	1.119	0.914	1.368	1.091	0.275	
Bouman (2002)	1.129	0.922	1.382	1.175	0.240	
Pooled	1.120	0.939	1.335	1.257	0.209	



(C) Hospital mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Zhang (2012)	1.035	0.790	1.356	0.249	0.803	
Bellomo (2009)	1.135	0.821	1.569	0.768	0.442	
Tolwani (2008)	0.995	0.768	1.289	-0.041	0.968	
Bouman (2002)	0.982	0.764	1.263	-0.139	0.889	
Pooled	1.025	0.809	1.297	0.203	0.839	

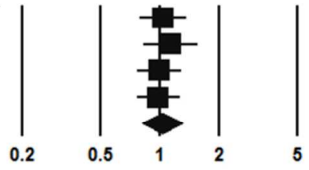


Figure 4

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Figure 5

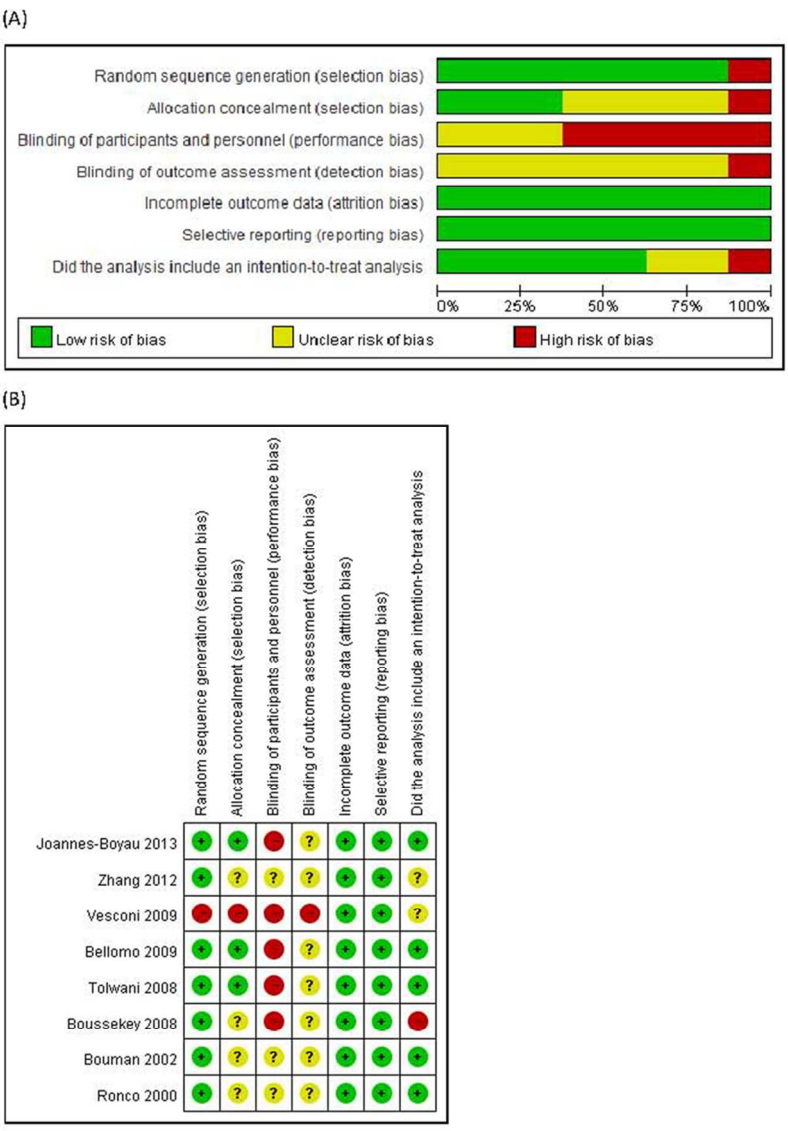

Figure 5

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PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

High- vs. low-dose hemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014171.R1
Article Type:	Research
Date Submitted by the Author:	24-Feb-2017
Complete List of Authors:	Li , Peng ; YantaiYuhuangding Hospital Qu, Li-ping ; YantaiYuhuangding Hospital, Department of Obstetrics Qi, Dong ; YantaiYuhuangding Hospital, Department of Nephrology Shen, Bo ; Zhongshan Hospital, Shanghai Medical College, Fudan University, Department of Nephrology Wang, Yi-mei ; Zhongshan Hospital, Shanghai Medical College, Fudan University Xu, Jia-rui ; Zhongshan Hospital, Shanghai Medical College, Fudan University Jiang, Wu-hua ; Zhongshan Hospital, Shanghai Medical College, Fudan University, Department of Nephrology Zhang, Hao ; Zhongshan Hospital, Shanghai Medical College, Fudan University Ding, Xiao-qiang ; Zhongshan Hospital, Shanghai Medical College, Fudan University, Department of Nephrology Teng, Jie
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Urology
Keywords:	acute kidney injury, dose, intensive care unit

High- vs. low-dose hemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis

Running title: Hemofiltration in acute kidney injury

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Word count: 2645

ABSTRACT

Objective: The purpose of this study was to perform a systematic review and meta-analysis to evaluate the effect of high-vs. low-dose hemofiltration on the survival of critically ill patients with acute kidney injury (AKI). We hypothesized that high-dose treatments are not associated with a higher risk of mortality.

Design: Meta-analysis.

Setting: Randomized controlled trials, and two-arm prospective and retrospective studies were included.

Participants: Critically ill patients with AKI.

Interventions: Continuous renal-replacement therapy.

Primary and secondary outcome measures: Primary outcomes: 90-day mortality, intensive care unit (ICU) mortality, hospital mortality; secondary outcomes: length of ICU and hospital stay.

Result: Eight studies including 2,970 patients were included in the analysis. Pooled results showed no significant difference in the 90-mortality rate between patients treated with high- or low-dose hemofiltration (pooled odds ratio [OR] = 0.899, 95% confidence interval [CI]: 0.728 to 1.109, P = 0.319). Findings were similar for ICU (pooled OR = 1.120, 95% CI: 0.939 to 1.335, P = 0.209) and hospital mortality (pooled OR = 1.025, 95% CI: 0.809 to 1.297, P = 0.839). Length of ICU and hospital stay were similar between high- and low-dose groups. Pooled results are not overly influenced by any one study, different cut-off points of prescribed dose, or different cut-off points of delivered dose. Meta-regression analysis indicated that the results were not affected by the percentage of patients with sepsis or septic shock.

Conclusion: High- and low-dose hemofiltration produce similar outcomes with respect to mortality and length of ICU and hospital stay in critically ill patients with AKI.

The study is registered at http://www.researchregistry.com/, registration number reviewregistry211.

Keywords: acute kidney injury, dose, intensive care unit, intensity, renal dialysis, renal-replacement therapy

Strengths and limitations of this study

- The strengths of this study are the inclusion of the most current literature, and the meta-regression analysis which evaluated the impact of patients with sepsis or septic shock on the overall pooled analysis.
- The limitation of this analysis is the considerable variation across the studies with regard to the prescribed doses for the high- and low-dose hemofiltration.

INTRODUCTION

Acute kidney injury (AKI) occurs in at least 5% of patients with who are admitted to the intensive care unit (ICU), and is an independent predictor of mortality.[1-3] In addition, about 50% of patients with septic shock will experience AKI.[4] The prognosis of patients with AKI is low, with a mortality rate of up to 70% despite improvements in hemodialysis and availability.[5-7]

Two methods for obtaining clearance in patients with AKI who require renal support are hemofiltration and hemodialysis. Hemofiltration uses convection to aid in the removal of middle molecular weight solutes, which is determined by the pore size of the membrane.[8] Hemofiltration is superior to hemodialysis in patients with AKI as it is believed that is can remove the toxic mediators of sepsis and inflammation.[8]

For patients who require RRT, the treatment dose or intensity may influence outcomes. Continuous renal replacement therapy (CRRT) in the form of hemofiltration is an option for treating patients with AKI, and may provide better clearance of toxic molecules, acid-base homeostasis, and removal of inflammatory mediators that can contribute to organ injury and dysfunction than other methods.[9-13] However, the optimum dosage of hemofiltration, including the ideal timing and dose is not clear. Some studies have reported benefits with intensive doses of CRRT with respect to mortality,[14,15] while others have not.[16-19]

Several prior systematic reviews and meta-analyses have assessed the use of CRRT for treating AKI. These studies found that high-dose CRRT was not associated with a decrease in mortality in patients with AKI.[20-22] Since the publication of these reviews, additional clinical studies have been published that addressed the use of CRRT in

AKI.[23,24] Prior reviews have addressed both hemofiltration and hemodialysis, which may not provide sufficient data with respect to either method.

Thus, the purpose of this study was to perform a systematic review and meta-analysis to evaluate the effect of high-vs. low-dose hemofiltration on the survival of critically ill patients with AKI. We hypothesized that high-dose treatments are not associated with a higher risk of mortality.

MATERIAL AND METHODS

Search strategy

This meta-analysis was performed according to the PRISMA guidelines. The study is registered at http://www.researchregistry.com/, and the registration number is reviewregistry211.

PubMed, Medline, Cochrane, Google Scholar databases were searched until June 22, 2016 using the following search terms: renal-replacement therapy, renal dialysis, acute kidney injury, intensive care unit, intensity, dose. Included studies were randomized controlled trials (RCTs), two-arm prospective, retrospective, or cohort studies that evaluated critically ill patients with AKI who received hemofiltration. Included studies had to report quantitative outcomes of interest. Letters, comments, editorials, case reports, proceeding, and personal communications were excluded. Studies that evaluated patients who had received previous RRT during the same hospital admission or who were on maintenance dialysis for end-stage kidney disease were excluded. The database searches were performed by two independent (two of the authors) reviewers. The authors independently reviewed all potential studies, and extracted data of interest. A third

reviewer was consulted to resolve any questions regarding inclusion of studies or data in the analysis, and a decision was arrived at by consensus.

Data extraction and quality assessment

The following information/ data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and the major outcomes of death up to 90-days (90 day mortality), ICU mortality, hospital mortality, and length of hospital or ICU stay.

The quality of the included studies was evaluated using the Cochran Risk of Bias tool outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions Version 5.1.0.[25]

Statistical analysis

Primary outcomes were 90-day mortality, ICU mortality, and hospital mortality. Secondary outcomes were length of ICU and hospital stay. Comparisons of the different mortality rates between patients receiving high- or low-dose hemofiltration were presented by odds ratio (OR) and 95% confidence interval (95% CI); an OR > 1 indicated that patients treated with high-intensity hemofiltration had a higher risk of death. The effect size of length of ICU and hospital stay was reported as difference in means; a difference in means > 0 indicated longer ICU or hospital stay in patients treated with high-dose hemofiltration. Pooled estimates for odds ratios and difference in means were

calculated using the DerSimonian and Laird random-effects model. A 2-sided P-value < 0.05 was considered statistically significant.

Heterogeneity was assessed using the Cochran Q and the I^2 statistic. For the Q statistic, $P < 0.10$ was considered statistically significant for heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity. The suggested ranges are as follows: no heterogeneity (I^2 = 0% to 25%), moderate heterogeneity (I^2 =25% to 50%), large heterogeneity (I^2 = 50% to 75%), and extreme heterogeneity (I^2 = 75% to 100%).

Sensitivity analysis was performed for the primary outcomes using the leave-one-out approach. Due to various definitions of high- and low-dose hemofiltration between the studies, additional sensitivity analysis was performed to examine the stability of pooled estimates according to various cut-off points of prescribed dose as well as the actual delivered dose. Meta-regression analysis was performed to examine whether the percentage of patients with sepsis or septic shock influenced the pooled estimates of the associations between hemofiltration and outcomes of interest. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

A total of 374 studies were identified in the initial search, of which 250 were excluded for being duplicate publications (Figure 1). Of the remaining 124 studies, 106 were excluded for not being relevant by review of title and/or abstract. The remaining 18 full-text

articles were examined, and 10 were excluded, the reasons for which are shown in Figure 1. Thus, eight studies were included in the meta-analysis.[14,16,17,19,23,24,26,27]

Of the eight studies, seven were RCTs [14,16,17,23,24,26] and one was a prospective study [27] (Table 1). A total of 2,970 patients were included, and the number of patients per study ranged from 19 to 1465. The mean patient age ranged from 59 to 73 years, over half of the patients were male (54% to 80%), and the causes for of AKI requiring RRT were sepsis, surgery (including cardiovascular surgery), and septic shock. Six of the eight studies reported mean APACHE II or III scores for the groups studied, and the mean scores were similar between the groups in the individual studies. The type of treatment, and the definition of high-dose or more-intensive therapy varied across the studies. The doses used also varied, ranging from 20 to 85 mL/kg/h.

Meta-analysis

Results of meta-analysis of the primary outcomes of within 90-day morality,[14,17,23,24] ICU mortality,[16,17,19,27] and hospital mortality [16,17,19,24] are presented in Figure 2. or low-dose hemofiltration mortality, There was low to moderate heterogeneity across the studies for each outcome ($Q = 4.10$, $P = 0.251$, $I^2 = 26.7\%$; $Q = 2.24$, $P = 0.524$, $I^2 = 0\%$; and $Q = 1.49$, $P = 0.686$, $I^2 = 0\%$, respectively).

No significant difference was found in the length of ICU stay between patients who received high- vs. low-dose treatment (pooled difference in means = -2.092, 95% CI = -5.638 to 1.453, $P = 0.247$) (Figure 2D). However, large heterogeneity was observed across the seven studies that reported data for length of ICU stay ($Q=25.10$, $P = 0.002$, $I^2 = 76.1\%$). The results were similar for length of hospital stay (pooled difference in means

= -0.034, 95% CI = -2.382 to 2.313, P = 0.977); however, no heterogeneity was observed for data regarding length of hospital stay (Q = 1.74, P = 0.784, I^2 = 0%) (Figure 2E).

Sensitivity analysis, meta-regression analysis, and quality assessment

Sensitivity analysis was performed in several ways. First, we used the leave-one-out approach to examine whether any single study influenced the pooled results of primary outcomes. The pooled results for the three primary outcomes did not significantly change when each study was removed in turn (Figure 3). Second, the use of various cut-off points of prescribed dose might minimize the influence of the various definitions of high- and low-dose in the included studies. Analysis indicated that the results were stable regardless of cut-off points of prescribed dose. Furthermore, we also performed analyses for the actual delivered dose with the same cut-off points, and the statistical significance was consistent when delivered dose was used in the analysis (Table 2). Taken together, these findings indicate that the pooled results are not overly influenced by any one study, different cut-off points of prescribed dose, or different cut-off points of delivered dose.

Meta-regression analysis was performed to examine whether patients with sepsis or septic shock affected the overall pooled analysis. The reason for the analysis was based on the fact that sepsis and septic shock differ in terms of blood pressure instability and possible emergent death. The results showed that the regression coefficients had a slope close to 0, indicating that the associations between RRT and selected outcomes were not influenced by the percentage of patients with sepsis or septic shock (P-values for all slope coefficients > 0.05) (Table 3).

Assessment of the quality of the included studies using the Cochran Risk of Bias tool indicated that there was low risk of bias for most of the studies (Figure S1A and S1B). One exception was the study of Vesconi et al., [27] which showed a high risk of selection, performance, and detection bias (Figure S1B). Overall, the included studies were of adequate quality.

Publication bias assessment was not performed due to limited number of included studies; 10 or more studies are necessary to assess publication bias.[28]

DISCUSSION

The purpose of this study was to conduct a systematic review and meta-analysis to examine the effect of hemofiltration dosage on mortality, length of hospital stay, and length of ICU stay in patients with AKI. For all outcomes examined, there was no difference between patients who received high- vs. low-dose hemofiltration. The results were consistent when the analyses used prescribed or delivered dose, and not influenced by the percentage of patients with sepsis or septic shock. Sensitivity analysis and quality assessment indicated no one study dominated the results, and that the included data was of adequate quality.

There results of this study are consistent with three prior meta-analyses, all of which found no survival benefit, or increased mortality, of high-dose CRRT in patients with acute renal failure.[20-22] Although, our findings are similar to prior studies, a strength of our analysis is the meta-regression analysis with evaluated the impact of patients with sepsis or septic shock on the overall pooled analysis. The meta-regression analysis indicated that heterogeneity due to a mixed population of sepsis and septic shock patients

did not influence the pooled results. In addition, we included two additional studies that were not included in the prior meta-analyses. The consistency of finding across the different meta-analyses, and findings of our meta-regression analysis, suggest that the delivered dose is not affected by the presence of systemic infection, and any variance seen when treating patients may reflect the severity of the acute kidney disease and/or an individual patient's condition.

The data from clinical studies on the benefit of high-dose hemofiltration in critically ill patients have been inconsistent. In 2000 Ronco et al.[14] reported improved survival with higher total effluent volumes (> 45 mL/kg/h) in patients with septic AKI , and in 2008, in a small pilot study, Boussekey et al.[26] found that high dose RRT was associated with an improved hemodynamic profile. However, that study did not find any significant effect on survival or organ dysfunction. In contrast, two randomized controlled multicenter studies found no added survival benefit of high-dose compared with standard-dose CRRT in critically ill patients with AKI.[17,18] A more recent study by Joannes-Boyau et al.[23] also found no evidence that high-dose (70 mL/kg/h) compared with standard-dose (35 ml/kg/h) RRT resulted in reduction in 28-day mortality, or to early improvements in hemodynamic profile or organ dysfunction in septic shock patients with AKI.[23]

A prior meta-analysis compared the efficacy of extended daily dialysis (EDD) and CCRT in treating patients with acute kidney injury. Zhang et al.[29] included 17 studies from 2000-2014 with a total of 1,208 patients. Meta-analysis of the included RCTs (n = 10) found no difference in mortality rates between EDD and CRRT (relative risk, 0.90; 95% CI, 0.74-1.11; P = 0.3). However, lower mortality risk was observed with EDD

compared with CRRT in observational studies (relative risk, 0.86; 95% CI, 0.74-1.00; P=0.05). For both RCTs and observational studies, recovery of kidney function, fluid removal, and days in the ICU were similar between procedures. The authors concluded that the findings from RCTs suggest that CRRT and EDD have similar efficacy, and that the difference in mortality observed in the analysis of the observational studies may be confounded by selection bias. The potential confounding effect of observational studies is also indicated by our quality assessment of the included studies which indicated that the observational study of Vesconi et al.[27] had a high risk of selection bias, as well as performance and detection bias.

The current analysis focused on hemofiltration. However, hemodialysis is also used to treat patients with AKI. Friedrich et al.[30] performed a meta-analysis in 2012 that included 19 RCTs that focused on the difference between hemofiltration and hemodialysis with similar doses. They found weak evidence supporting the increased clearance of medium to large molecules by hemofiltration compared to hemodialysis, but there was no difference in mortality between the two methods. No dose comparison was performed in their study.

Our study was limited by the considerable variation across the studies with regard to the prescribed doses for high- and low-dose hemofiltration. It is difficult to standardize the prescribed and delivered doses across the studies due to differences in equipment used and personnel. There was also a wide range of effect size, and several of the studies reported opposite findings. In addition, only four of the included studies reported data for the primary endpoint of mortality within 90-days, and not all the studies were RCTs. In addition, due to the heterogeneity of dosing across studies, the differences in the

definition of high-dose, and the fact that the raw data for each group was not presented, it was difficult to group the analysis according to a cut-off value of the standard of care dose of 35 mL/kg/hr. For example, Vesconi et al.[27] defined 35mL/kg/h as “more intensive” and compared the finding of that dosing with “less intensive” < 20 to 34 mL/kg/h. This differ, for example, of the study by Zhang et al.[29] which compared 85 mL/kg/h with 50 mL/kg/hr. It is highly possible that this variability may have confounded our results. However, sensitivity analysis found that no one study overly influences the findings; thus suggesting that although heterogeneity in dosing was present, the pooled results are robust. In addition, six of the eight studies reported mean APACHE II or III scores for the groups studied, and the mean scores were similar between the groups in the individual studies, indicating that the illness severity was similar between the groups in each of these six studies. Subgroup analyses of different covariates, such as according to renal function, would aid in the analysis; however, due to limited availability of raw data few variables can be investigated. Lastly, our original intention was to perform a meta-analysis examining the outcomes of using different doses of renal replacement therapy and during our initial literature search we included all modalities of CRRT. However, we found that the majority of studies that compared different dosages used hemofiltration rather than other modalities. For this reason we limited the analysis to hemofiltration.

This results of this meta-analysis found that mortality rates and length of ICU and hospital stay were not different between critically ill patients with AKI who received high- or low-dose hemofiltration. However, additional well-designed studies are necessary to further investigate what is the optimal CRRT for critically ill patients with AKI.

Acknowledgements

We would like to express our sincere gratitude to our colleagues whose names did not appear as authors, but also contributed to the study. We especially thank Xiao Tan, Jifu Jin, and Zhouping Zou for collecting the data.

Funding source

Key Project in the National Science & Technology Pillar Program in the Twelfth Five-year Plan Period (2011BAI10B07); Scientific Research Project of Shanghai Committee of Science and Technology (12DJ1400201).

Competing interests: None

Author contributions:

PL: study design, literature research, manuscript preparation; LPQ: study design, literature research, manuscript preparation; DQ: manuscript preparation, data acquisition, data analysis; BS: manuscript preparation, data acquisition, data analysis; YW: manuscript preparation, data acquisition, data analysis; JRX: manuscript preparation, data acquisition, data analysis; WHJ: data analysis, statistical analysis; HZ: data analysis, statistical analysis; XQD: guarantor of integrity of the entire study, study concepts; JT: study concepts, study design, guarantor of integrity of the entire, study, manuscript editing

Ethics approval: Meta-analyses do not require ethical approval as no experiments on humans or animals are performed.

Informed Consent: Not applicable

Data sharing statement: No additional data available

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram of study selection.

Figure 2. Meta-analysis for treatment effect of hemofiltration on (A) mortality within 90 days, (B) ICU mortality, (C) in hospital mortality, (D) length of ICU stay, and (E) length of hospital stay.

Figure 3. Sensitivity analysis using leave-one-out approach for the treatment effect of hemofiltration (A) mortality within 90 days, (B) ICU mortality, and (C) in hospital mortality.

Figure S1. Quality assessment.

Table 1. Summary of basic characteristics of studies included in the for meta-analysis

Study	Study design	Number of patients	Treatment	Prescribed dose (mL/kg/h)	Delivered dose (mL/kg/h)	Duration (days)	Age (yrs)	Male (%)	Major cause of AKI	Sepsis	Oliguria	Mean APACHE II score
Joannes-Boyau (2013)	RCT	66	High-volume HF	70	65.6 (40–67.9)*	96 hrs	68 (58–77)*	68.0 %	Sepsis	66 (100%)		
		71	Standard-volume HF	35	33.2 (28.7–33.6)*		70 (58–75)*	54.0 %		71 (100%)		
Vesconi (2009)	Prospective	75	More-intensive	35	44.8 (9.4)	2 (1–3)*	61.01 (17.4)	58.1 %		33 (40.5%)	36 (48.6%)	
		202	Less-intensive	21-34	26.9 (4.0)	4 (2–8)*	63.48 (15.9)	67.8 %	Surgery	81 (40.1%)	84 (41.7%)	
		61	Less-intensive	20	15.4 (4.2)	3 (2–6)*	59.05 (19.0)	73.8 %		19 (31.2%)	30 (49.5%)	
Zhang (2012)	RCT	141	EHVHF	85	87.54 (12.54)	9.38 (12. 06)	56.62 (16.38)	58.9 %	Septic shock	72 (51.06%)		21.97
		139	HVHF	50	49.99 (9.65)	8.88 (10.79)	59.96 (18.81)	64.0 %		69 (49.64%)		22.6
Bouman (2002)	RCT	35	EHV	72	48.2 (42.3–58.7)*	68.5 (28.0–140.8)*,†	68 (13)	60.0 %			35 (100%)	23.5
		35	ELV	24-36	20.1 (17.5–22.0)*	94.0 (53.0–181.5)*,†	70 (10)	57.0 %	Cardiac surgery		35 (100%)	21.7
		36	LLV	24-36	19.0 (16.6–21.2)*	69.5 (28.3–157.7)*,†	67 (13)	61.0 %			30 (100%)	23.6
Tolwani (2008)	RCT	100	High Dosage	35	29	10.0 (9.8)	58 (16)	59.0 %	Septic shock	54 (54%)	64 (64%)	26
		100	Standard Dosage	20	17	9.7 (11.3)	62 (15)	57.0 %		54 (54%)	63 (63%)	26
Bellomo (2009)	RCT	722	Higher-Intensity CRRT	40	33.4 (12.8)	6.3 (8.7)	64.7(14.5)	65.7 %	Sepsis	360 (49.9)	430 (59.6%)	102.5‡
		743	Lower-Intensity CRRT	25	22 (17.8)	5.9 (7.7)	64.4 (15.3)	63.5 %		363 (48.9)	444 (59.8%)	102.3‡
Boussekey (2008)	RCT	9	HVHF	65	62	7 (2–17)*	68 (58–74)*	78.0 %	Sepsis	9 (100 %)		31
		10	LVHF	35	32	6 (2–14)*	72.5 (54–77)*	80.0 %		10 (100%)		33.5
Ronco (2000)	RCT	146		20			61 (10)	55.5 %		20 (14%)		22
		139		35			59 (9)	55.4 %	Surgery	17 (12%)		24
		140		45			63 (12)	57.1 %		15 (11%)		22

AKI, acute kidney injury; CRRT, continuous renal-replacement therapy; EHV, early high-volume hemofiltration; EHVHF, extra high-volume hemofiltration; ELV, early low-volume hemofiltration; HVHF, high-volume hemofiltration; LLV, late low-volume hemofiltration LVHF, low-volume hemofiltration; RCT, randomized controlled trial.,

*Data were presented by median and inter-quartile range (IQR), and by mean and standard deviation (SD) if not specified.

†Numbers were shown in hours.

‡Measured by APACHE III.

Table 2. Sensitivity-analysis for treatment effect on mortality according to different cut-off points of prescribed dose and delivered dose

	Number of studies included	Pooled odds ratio	Lower limit	Upper limit	Z-Value	P-Value
Prescribed dose						
(A) 90-day mortality						
50 mL/kg/h	2	0.969	0.655	1.434	-0.156	0.876
40 mL/kg/h	3	0.831	0.500	1.382	-0.712	0.476
30 mL/kg/h	2	0.729	0.385	1.381	-0.970	0.332
(B) ICU mortality						
50 mL/kg/h	1	1.199	0.584	2.465	0.495	0.621
40 mL/kg/h	2	1.039	0.845	1.278	0.365	0.715
30 mL/kg/h	3	1.129	0.922	1.382	1.175	0.240
(C) Hospital mortality						
50 mL/kg/h	2	1.112	0.751	1.647	0.532	0.595
40 mL/kg/h	2	1.015	0.709	1.453	0.080	0.936
30 mL/kg/h	2	0.978	0.728	1.314	-0.145	0.884
Delivered dose						
(A) 90-day mortality						
50 mL/kg/h	2	0.969	0.655	1.434	-0.156	0.876
40 mL/kg/h	1	1.240	0.633	2.431	0.628	0.530
30 mL/kg/h*	1	0.997	0.811	1.225	-0.033	0.974
(B) ICU mortality						
50 mL/kg/h	1	1.199	0.584	2.465	0.495	0.621
40 mL/kg/h	2	1.385	0.961	1.996	1.746	0.081
30 mL/kg/h	2	1.163	0.837	1.616	0.900	0.368

(C) Hospital mortality

50 mL/kg/h	1	0.993	0.613	1.608	-0.029	0.977
40 mL/kg/h	1	1.391	0.707	2.735	0.957	0.339
30 mL/kg/h	1	0.913	0.647	1.288	-0.521	0.602

*Ronco et al. (2000) did not provide information on delivered dose of continuous renal replacement therapy, and therefore was excluded.

Table 3. Meta-regression analysis for each outcome

Outcome	Intercept[a]	Slope[a]
Mortality within 90 days	-0.416 (0.191)	0.007 (0.004)
ICU mortality	0.306 (0.346)	-0.004 (0.007)
Hospital mortality	0.305 (0.344)	-0.006 (0.007)
Length of ICU stay	-2.889 (1.901)	0.030 (0.038)
Length of hospital stay	-1.739 (4.133)	0.035 (0.081)

[a]Presented as point estimate of coefficient and standard error.

Figure 1

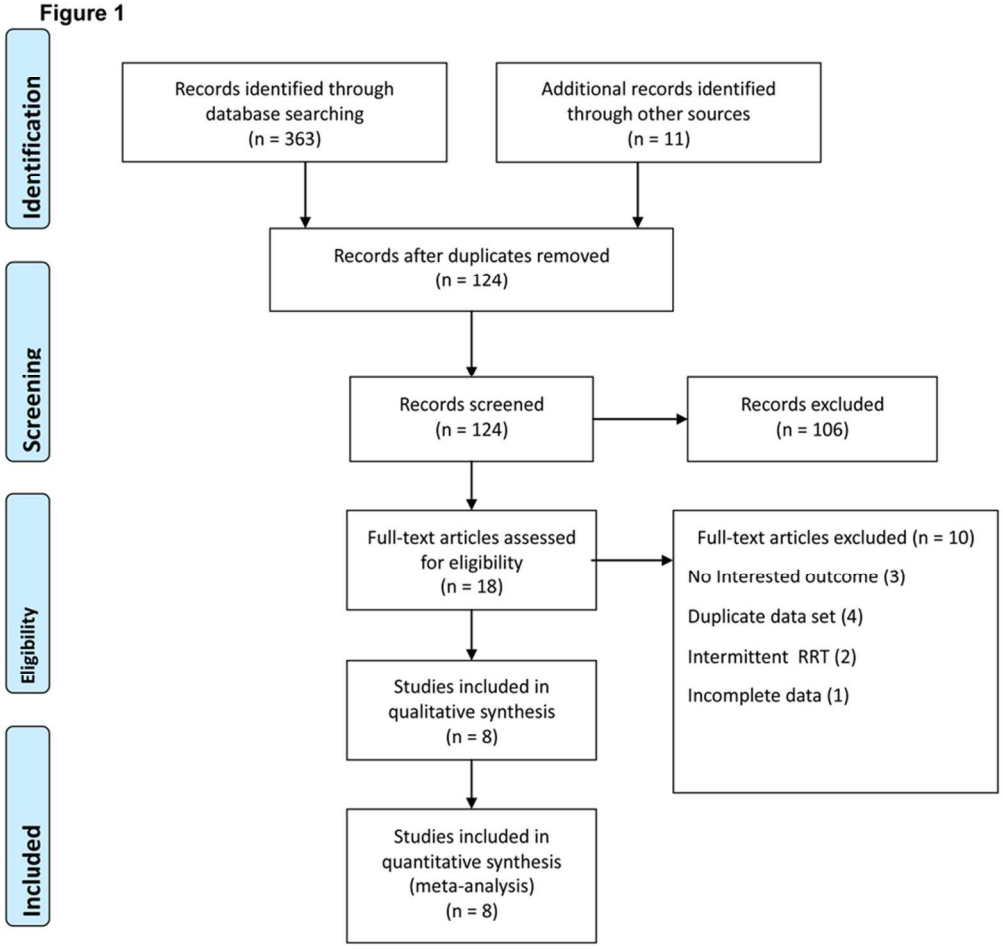
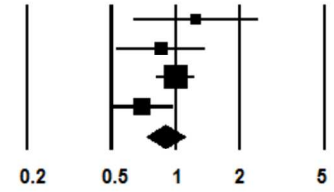


Figure 1

80x79mm (300 x 300 DPI)

(A) 90-day mortality

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	1.240	0.633	2.431	0.628	0.530
Zhang (2012)	0.854	0.528	1.383	-0.642	0.521
Bellomo (2009)	0.997	0.811	1.225	-0.033	0.974
Ronco (2000)	0.696	0.498	0.972	-2.125	0.034
Pooled	0.899	0.728	1.109	-0.996	0.319



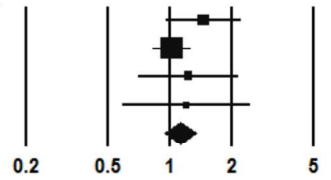
Heterogeneity test: Q = 4.10, P = 0.251, I^2 = 26.7%

Figure 2A

380x144mm (96 x 96 DPI)

(B) ICU mortality

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Vesconi (2009)	1.456	0.953	2.225	1.735	0.083
Bellomo (2009)	1.026	0.827	1.273	0.233	0.816
Tolwani (2008)	1.227	0.700	2.152	0.715	0.475
Bouman (2002)	1.199	0.584	2.465	0.495	0.621
Pooled	1.120	0.939	1.335	1.257	0.209



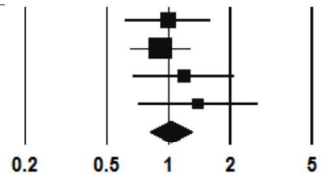
Heterogeneity test: Q = 2.24, P = 0.524, I^2 = 0%

Figure 2B

382x142mm (96 x 96 DPI)

(C) Hospital mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhang (2012)	0.993	0.613	1.608	-0.029	0.977
Bellomo (2009)	0.913	0.647	1.288	-0.521	0.602
Tolwani (2008)	1.185	0.669	2.099	0.583	0.560
Bouman (2002)	1.391	0.707	2.735	0.957	0.339
Pooled	1.025	0.809	1.297	0.203	0.839



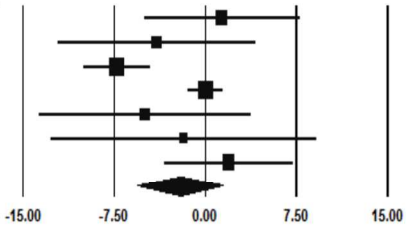
Heterogeneity test: Q = 1.49, P = 0.686, I^2 = 0%

Figure 2C

382x143mm (96 x 96 DPI)

(D) Length of ICU stay

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	1.330	-5.076	7.736	0.407	0.684
Zhang (2012)	-4.010	-12.141	4.121	-0.967	0.334
Vesconi (2009)	-7.300	-10.003	-4.596	-5.292	0.000
Bellomo (2009)	0.000	-1.449	1.449	0.000	1.000
Tolwani (2008)	-5.000	-13.704	3.704	-1.126	0.260
Boussekey (2008)	-1.840	-12.765	9.085	-0.330	0.741
Bouman (2002)	1.910	-3.417	7.236	0.703	0.482
Pooled	-2.092	-5.638	1.453	-1.157	0.247



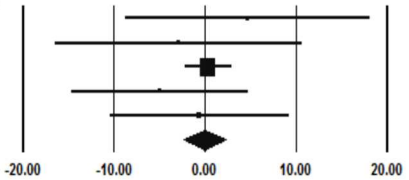
Heterogeneity test: Q = 25.10, P < 0.001, I^2 = 76.1%

Figure 2D

430x177mm (96 x 96 DPI)

(E) Length of hospital stay

Study name	Statistics for each study				
	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	4.630	-8.836	18.096	0.674	0.500
Zhang (2012)	-2.940	-16.517	10.637	-0.424	0.671
Bellomo (2009)	0.300	-2.286	2.886	0.227	0.820
Tolwani (2008)	-5.000	-14.644	4.644	-1.016	0.310
Bouman (2002)	-0.673	-10.525	9.178	-0.134	0.893
Pooled	-0.034	-2.382	2.313	-0.029	0.977



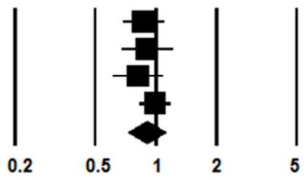
Heterogeneity test: Q = 1.74, P = 0.784, I^2 = 0%

Figure 2E

430x158mm (96 x 96 DPI)

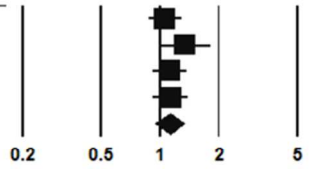
(A) 90-day mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Joannes-Boyau (2013)	0.867	0.686	1.096	-1.195	0.232	
Zhang (2012)	0.906	0.679	1.209	-0.672	0.502	
Bellomo (2009)	0.815	0.612	1.085	-1.403	0.161	
Ronco (2000)	0.991	0.825	1.189	-0.102	0.919	
Pooled	0.899	0.728	1.109	-0.996	0.319	



(B) ICU mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Vesconi (2009)	1.060	0.873	1.287	0.589	0.556	
Bellomo (2009)	1.336	0.984	1.815	1.854	0.064	
Tolwani (2008)	1.119	0.914	1.368	1.091	0.275	
Bouman (2002)	1.129	0.922	1.382	1.175	0.240	
Pooled	1.120	0.939	1.335	1.257	0.209	



(C) Hospital mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Zhang (2012)	1.035	0.790	1.356	0.249	0.803	
Bellomo (2009)	1.135	0.821	1.569	0.768	0.442	
Tolwani (2008)	0.995	0.768	1.289	-0.041	0.968	
Bouman (2002)	0.982	0.764	1.263	-0.139	0.889	
Pooled	1.025	0.809	1.297	0.203	0.839	

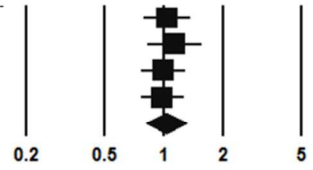


Figure 3

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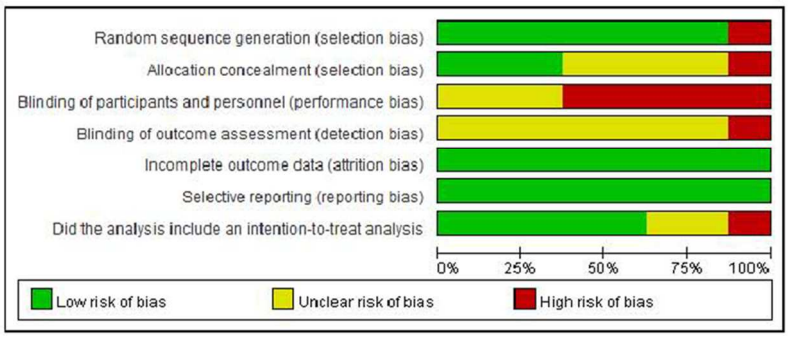
Figure S1

(A)



(B)

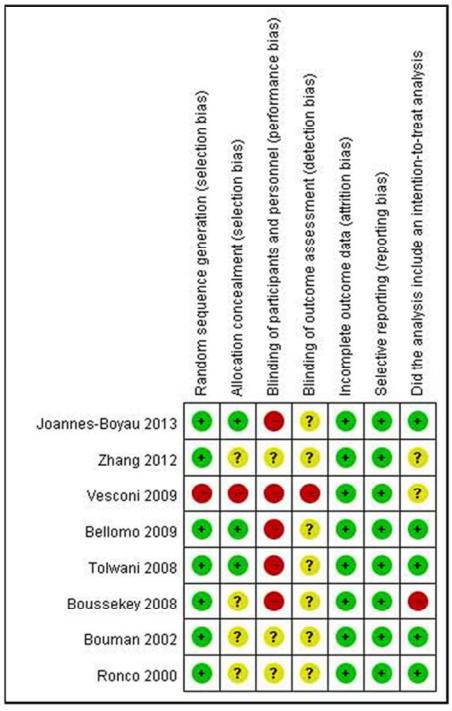


Figure S1

80x113mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

High- vs. low-dose hemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014171.R2
Article Type:	Research
Date Submitted by the Author:	14-Apr-2017
Complete List of Authors:	Li , Peng ; YantaiYuhuangding Hospital Qu, Li-ping ; YantaiYuhuangding Hospital, Department of Obstetrics Qi, Dong ; YantaiYuhuangding Hospital, Department of Nephrology Shen, Bo ; Zhongshan Hospital, Shanghai Medical College, Fudan University, Department of Nephrology Wang, Yi-mei ; Zhongshan Hospital, Shanghai Medical College, Fudan University Xu, Jia-rui ; Zhongshan Hospital, Shanghai Medical College, Fudan University Jiang, Wu-hua ; Zhongshan Hospital, Shanghai Medical College, Fudan University, Department of Nephrology Zhang, Hao ; Zhongshan Hospital, Shanghai Medical College, Fudan University Ding, Xiao-qiang ; Zhongshan Hospital, Shanghai Medical College, Fudan University, Department of Nephrology Teng, Jie
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Urology
Keywords:	acute kidney injury, dose, intensive care unit

High- vs. low-dose hemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis

Running title: Hemofiltration in acute kidney injury

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Word count: 2719

ABSTRACT

Objective: The purpose of this study was to perform a systematic review and meta-analysis to evaluate the effect of high-vs. low-dose hemofiltration on the survival of critically ill patients with acute kidney injury (AKI). We hypothesized that high-dose treatments are not associated with a higher risk of mortality.

Design: Meta-analysis.

Setting: Randomized controlled trials, and two-arm prospective and retrospective studies were included.

Participants: Critically ill patients with AKI.

Interventions: Continuous renal-replacement therapy.

Primary and secondary outcome measures: Primary outcomes: 90-day mortality, intensive care unit (ICU) mortality, hospital mortality; secondary outcomes: length of ICU and hospital stay.

Result: Eight studies including 2,970 patients were included in the analysis. Pooled results showed no significant difference in the 90-mortality rate between patients treated with high- or low-dose hemofiltration (pooled odds ratio [OR] = 0.90, 95% confidence interval [CI]: 0.73 to 1.11, P = 0.32). Findings were similar for ICU (pooled OR = 1.12, 95% CI: 0.94 to 1.34, P = 0.21) and hospital mortality (pooled OR = 1.03, 95% CI: 0.81 to 1.30, P = 0.84). Length of ICU and hospital stay were similar between high- and low-dose groups. Pooled results are not overly influenced by any one study, different cut-off points of prescribed dose, or different cut-off points of delivered dose. Meta-regression analysis indicated that the results were not affected by the percentage of patients with sepsis or septic shock.

Conclusion: High- and low-dose hemofiltration produce similar outcomes with respect to mortality and length of ICU and hospital stay in critically ill patients with AKI.

This study was not registered at the time the data were collected and analyzed. It has since been registered on February 17, 2017 at http://www.researchregistry.com/, registration number: reviewregistry211.

Keywords: acute kidney injury, dose, intensive care unit, intensity, renal dialysis, renal-replacement therapy

Strengths and limitations of this study

- The strengths of this study are the inclusion of the most current literature, and the meta-regression analysis which evaluated the impact of patients with sepsis or septic shock on the overall pooled analysis.
- The limitation of this analysis is the considerable variation across the studies with regard to the prescribed doses for the high- and low-dose hemofiltration.

INTRODUCTION

Acute kidney injury (AKI) occurs in at least 5% of patients with who are admitted to the intensive care unit (ICU), and is an independent predictor of mortality.[1-3] In addition, about 50% of patients with septic shock will experience AKI.[4] The prognosis of patients with AKI is low, with a mortality rate of up to 70% despite improvements in hemodialysis and availability.[5-7]

Two methods for obtaining clearance in patients with AKI who require renal support are hemofiltration and hemodialysis. Hemofiltration uses convection to aid in the removal of middle molecular weight solutes, which is determined by the pore size of the membrane.[8] Hemofiltration is believed to be superior to hemodialysis in patients with AKI as it is thought it can remove the toxic mediators of sepsis and inflammation.[8]

For patients who require RRT, the treatment dose or intensity may influence outcomes. Continuous renal replacement therapy (CRRT) in the form of hemofiltration is an option for treating patients with AKI, and may provide better clearance of toxic molecules, acid-base homeostasis, and removal of inflammatory mediators that can contribute to organ injury and dysfunction than other methods.[9-13] However, the optimum dosage of hemofiltration, including the ideal timing and dose is not clear. Some studies have reported benefits with intensive doses of CRRT with respect to mortality,[14,15] while others have not.[16-19]

Several prior systematic reviews and meta-analyses have assessed the use of CRRT for treating AKI. These studies found that high-dose CRRT was not associated with a decrease in mortality in patients with AKI.[20-22] Since the publication of these reviews, additional clinical studies have been published that addressed the use of CRRT in

AKI.[23,24] Prior reviews have addressed both hemofiltration and hemodialysis, which may not provide sufficient data with respect to either method.

Thus, the purpose of this study was to perform a systematic review and meta-analysis to evaluate the effect of high-vs. low-dose hemofiltration on the survival of critically ill patients with AKI. We hypothesized that high-dose treatments are not associated with a higher risk of mortality.

MATERIAL AND METHODS

Search strategy

This meta-analysis was performed according to the PRISMA guidelines. This study was not registered at the time the data were collected and analyzed. It has since been registered on February 17, 2017 at http://www.researchregistry.com/, registration number: reviewregistry211.

PubMed, Medline, Cochrane, Google Scholar databases were searched until June 22, 2016 using the following search terms: renal-replacement therapy, renal dialysis, acute kidney injury, intensive care unit, intensity, dose. Included studies were randomized controlled trials (RCTs), two-arm prospective, retrospective, or cohort studies that evaluated critically ill patients with AKI who received hemofiltration. Included studies had to report quantitative outcomes of interest. Letters, comments, editorials, case reports, proceeding, and personal communications were excluded. Studies that evaluated patients who had received previous RRT during the same hospital admission or who were on maintenance dialysis for end-stage kidney disease were excluded. The database searches were performed by two independent (two of the authors) reviewers. The authors

independently reviewed all potential studies, and extracted data of interest. A third reviewer was consulted to resolve any questions regarding inclusion of studies or data in the analysis, and a decision was arrived at by consensus.

Data extraction and quality assessment

The following information/ data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and the major outcomes of death up to 90-days (90 day mortality), ICU mortality, hospital mortality, and length of hospital or ICU stay.

The quality of the included studies was evaluated using the Cochran Risk of Bias tool outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions Version 5.1.0.[25]

Statistical analysis

Primary outcomes were 90-day mortality, ICU mortality, and hospital mortality. Secondary outcomes were length of ICU and hospital stay. Comparisons of the different mortality rates between patients receiving high- or low-dose hemofiltration were presented by odds ratio (OR) and 95% confidence interval (95% CI); an OR > 1 indicated that patients treated with high-intensity hemofiltration had a higher risk of death. The effect size of length of ICU and hospital stay was reported as difference in means; a difference in means > 0 indicated longer ICU or hospital stay in patients treated with high-dose hemofiltration. Pooled estimates for odds ratios and difference in means were

calculated using the DerSimonian and Laird random-effects model. A 2-sided P-value < 0.05 was considered statistically significant.

Heterogeneity was assessed using the Cochran Q and the I^2 statistic. For the Q statistic, $P < 0.10$ was considered statistically significant for heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity. The suggested ranges are as follows: no heterogeneity (I^2 = 0% to 25%), moderate heterogeneity (I^2 =25% to 50%), large heterogeneity (I^2 = 50% to 75%), and extreme heterogeneity (I^2 = 75% to 100%).

Sensitivity analysis was performed for the primary outcomes using the leave-one-out approach. Due to various definitions of high- and low-dose hemofiltration between the studies, additional sensitivity analysis was performed to examine the stability of pooled estimates according to various cut-off points of prescribed dose as well as the actual delivered dose. Meta-regression analysis was performed to examine whether the percentage of patients with sepsis or septic shock influenced the pooled estimates of the associations between hemofiltration and outcomes of interest. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

A total of 374 studies were identified in the initial search, of which 250 were excluded for being duplicate publications (Figure 1). Of the remaining 124 studies, 106 were excluded for not being relevant by review of title and/or abstract. The remaining 18 full-text

articles were examined, and 10 were excluded, the reasons for which are shown in Figure 1. Thus, eight studies were included in the meta-analysis.[14,16,17,19,23,24,26,27]

Of the eight studies, seven were RCTs [14,16,17,23,24,26] and one was a prospective study [27] (Table 1). A total of 2,970 patients were included, and the number of patients per study ranged from 19 to 1465. The mean patient age ranged from 59 to 73 years, over half of the patients were male (54% to 80%), and the causes for of AKI requiring RRT were sepsis, surgery (including cardiovascular surgery), and septic shock. Six of the eight studies reported mean APACHE II or III scores for the groups studied, and the mean scores were similar between the groups in the individual studies. The type of treatment, and the definition of high-dose or more-intensive therapy varied across the studies. The doses used also varied, with low-dose ranging from 20 to 36 mL/kg/h and high-dose ranging from 35 to 85 mL/kg/h.

Meta-analysis

Results of meta-analysis of the primary outcomes of within 90-day morality,[14,17,23,24] ICU mortality,[16,17,19,27], and hospital mortality [16,17,19,24] are presented in Figure 2. The pooled results showed no significant difference in the 90-mortality rate between patients treated with high- or low-dose hemofiltration (pooled OR = 0.90, 95% CI: 0.73 to 1.11, P = 0.32) (Figure 2A). The findings were similar for ICU mortality (pooled OR = 1.12, 95% CI: 0.94 to 1.34, P = 0.21) and hospital mortality (pooled OR = 1.02, 95% CI: 0.81 to 1.30, P = 0.84) (Figure 2B, C). There was low to moderate heterogeneity across the studies for each outcome (Q = 4.10, P = 0.25, I^2 = 26.7%; Q = 2.24, P = 0.52, I^2 = 0%; and Q = 1.49, P = 0.69, I^2 = 0%, respectively).

No significant difference was found in the length of ICU stay between patients who received high- vs. low-dose treatment (pooled difference in means = -2.09, 95% CI: -5.64 to 1.45, P = 0.25) (Figure 2D). However, large heterogeneity was observed across the seven studies that reported data for length of ICU stay (Q = 25.10, P < 0.001, I^2 = 76.1%). The results were similar for length of hospital stay (pooled difference in means = -0.03, 95% CI: -2.38 to 2.31, P = 0.98); however, no heterogeneity was observed for data regarding length of hospital stay (Q = 1.74, P = 0.78, I^2 = 0%) (Figure 2E).

Sensitivity analysis, meta-regression analysis, and quality assessment

Sensitivity analysis was performed in several ways. First, we used the leave-one-out approach to examine whether any single study influenced the pooled results of primary outcomes. The pooled results for the three primary outcomes did not significantly change when each study was removed in turn (Figure 3). Second, the use of various cut-off points of prescribed dose might minimize the influence of the various definitions of high- and low-dose in the included studies. Analysis indicated that the results were stable regardless of cut-off points of prescribed dose. Furthermore, we also performed analyses for the actual delivered dose with the same cut-off points, and the statistical significance was consistent when delivered dose was used in the analysis (Table 2). Taken together, these findings indicate that the pooled results are not overly influenced by any one study, different cut-off points of prescribed dose, or different cut-off points of delivered dose.

Meta-regression analysis was performed to examine whether patients with sepsis or septic shock affected the overall pooled analysis. The reason for the analysis was based on the fact that sepsis and septic shock differ in terms of blood pressure instability and

possible emergent death. The results showed that the regression coefficients had a slope close to 0, indicating that the associations between RRT and selected outcomes were not influenced by the percentage of patients with sepsis or septic shock (P-values for all slope coefficients > 0.05) (Table 3).

Assessment of the quality of the included studies using the Cochran Risk of Bias tool indicated that there was low risk of bias for most of the studies (Figure S1A and S1B). One exception was the study of Vesconi et al., [27] which showed a high risk of selection, performance, and detection bias (Figure S1B). Overall, the included studies were of adequate quality.

Publication bias assessment was not performed due to limited number of included studies; 10 or more studies are necessary to assess publication bias.[28]

DISCUSSION

The purpose of this study was to conduct a systematic review and meta-analysis to examine the effect of hemofiltration dosage on mortality, length of hospital stay, and length of ICU stay in patients with AKI. For all outcomes examined, there was no difference between patients who received high- vs. low-dose hemofiltration. The results were consistent when the analyses used prescribed or delivered dose, and not influenced by the percentage of patients with sepsis or septic shock. Sensitivity analysis and quality assessment indicated no one study dominated the results, and that the included data was of adequate quality.

There results of this study are consistent with three prior meta-analyses, all of which found no survival benefit, or increased mortality, of high-dose CRRT in patients with

acute renal failure.[20-22] Although, our findings are similar to prior studies, a strength of our analysis is the meta-regression analysis with evaluated the impact of patients with sepsis or septic shock on the overall pooled analysis. The meta-regression analysis indicated that heterogeneity due to a mixed population of sepsis and septic shock patients did not influence the pooled results. In addition, we included two additional studies that were not included in the prior meta-analyses. The consistency of finding across the different meta-analyses, and findings of our meta-regression analysis, suggest that the delivered dose is not affected by the presence of systemic infection, and any variance seen when treating patients may reflect the severity of the acute kidney disease and/or an individual patient's condition.

The data from clinical studies on the benefit of high-dose hemofiltration in critically ill patients have been inconsistent. In 2000 Ronco et al.[14] reported improved survival with higher total effluent volumes (> 45 mL/kg/h) in patients with septic AKI , and in 2008, in a small pilot study, Boussekey et al.[26] found that high dose RRT was associated with an improved hemodynamic profile. However, that study did not find any significant effect on survival or organ dysfunction. In contrast, two randomized controlled multicenter studies found no added survival benefit of high-dose compared with standard-dose CRRT in critically ill patients with AKI.[17,18] A more recent study by Joannes-Boyau et al.[23] also found no evidence that high-dose (70 mL/kg/h) compared with standard-dose (35 ml/kg/h) RRT resulted in reduction in 28-day mortality, or to early improvements in hemodynamic profile or organ dysfunction in septic shock patients with AKI.[23]

A prior meta-analysis compared the efficacy of extended daily dialysis (EDD) and CCRT in treating patients with acute kidney injury. Zhang et al.[29] included 17 studies from 2000-2014 with a total of 1,208 patients. Meta-analysis of the included RCTs (n = 10) found no difference in mortality rates between EDD and CRRT (relative risk, 0.90; 95% CI, 0.74-1.11; P = 0.3). However, lower mortality risk was observed with EDD compared with CRRT in observational studies (relative risk, 0.86; 95% CI, 0.74-1.00; P=0.05). For both RCTs and observational studies, recovery of kidney function, fluid removal, and days in the ICU were similar between procedures. The authors concluded that the findings from RCTs suggest that CRRT and EDD have similar efficacy, and that the difference in mortality observed in the analysis of the observational studies may be confounded by selection bias. The potential confounding effect of observational studies is also indicated by our quality assessment of the included studies which indicated that the observational study of Vesconi et al.[27] had a high risk of selection bias, as well as performance and detection bias.

The current analysis focused on hemofiltration. However, hemodialysis is also used to treat patients with AKI. Friedrich et al.[30] performed a meta-analysis in 2012 that included 19 RCTs that focused on the difference between hemofiltration and hemodialysis with similar doses. They found weak evidence supporting the increased clearance of medium to large molecules by hemofiltration compared to hemodialysis, but there was no difference in mortality between the two methods. No dose comparison was performed in their study.

Our study was limited by the considerable variation across the studies with regard to the prescribed doses for high- and low-dose hemofiltration. It is difficult to standardize

the prescribed and delivered doses across the studies due to differences in equipment used and personnel. There was also a wide range of effect size, and several of the studies reported opposite findings. In addition, only four of the included studies reported data for the primary endpoint of mortality within 90-days, and not all the studies were RCTs. In addition, due to the heterogeneity of dosing across studies, the differences in the definition of high-dose, and the fact that the raw data for each group was not presented, it was difficult to group the analysis according to a cut-off value of the standard of care dose of 35 mL/kg/hr. For example, Vesconi et al.[27] defined 35mL/kg/h as "more intensive" and compared the finding of that dosing with "less intensive" < 20 to 34 mL/kg/h. This differed, for example, from the study by Zhang et al.[29] which compared 85 mL/kg/h with 50 mL/kg/hr. It is highly possible that this variability may have confounded our results. However, sensitivity analysis found that no one study overly influences the findings; thus suggesting that although heterogeneity in dosing was present, the pooled results are robust. In addition, six of the eight studies reported mean APACHE II or III scores for the groups studied, and the mean scores were similar between the groups in the individual studies, indicating that the illness severity was similar between the groups in each of these six studies. Subgroup analyses of different covariates, such as according to renal function, would aid in the analysis; however, due to limited availability of raw data few variables can be investigated. Lastly, our original intention was to perform a meta-analysis examining the outcomes of using different doses of renal replacement therapy and during our initial literature search we included all modalities of CRRT. However, we found that the majority of studies that compared

different dosages used hemofiltration rather than other modalities. For this reason we limited the analysis to hemofiltration.

This results of this meta-analysis found that mortality rates and length of ICU and hospital stay were not different between critically ill patients with AKI who received high- or low-dose hemofiltration.

Acknowledgements

We would like to express our sincere gratitude to our colleagues whose names did not appear as authors, but also contributed to the study. We especially thank Xiao Tan, Jifu Jin, and Zhouping Zou for collecting the data.

Funding source

Key Project in the National Science & Technology Pillar Program in the Twelfth Five-year Plan Period (2011BAI10B07); Scientific Research Project of Shanghai Committee of Science and Technology (12DJ1400201); the Use of Early Intervention Techniques and Specification in CKD (2013SY048)

Competing interests: None

Author contributions:

PL: study design, literature research, manuscript preparation; LPQ: study design, literature research, manuscript preparation; DQ: manuscript preparation, data acquisition, data analysis; BS: manuscript preparation, data acquisition, data analysis; YW: manuscript preparation, data acquisition, data analysis; JRX: manuscript preparation, data acquisition, data analysis; WHJ: data analysis, statistical analysis; HZ: data analysis, statistical analysis; XQD: guarantor of integrity of the entire study, study concepts; JT:

study concepts, study design, guarantor of integrity of the entire, study, manuscript editing

Ethics approval: Meta-analyses do not require ethical approval as no experiments on humans or animals are performed.

Informed Consent: Not applicable

Data sharing statement: No additional data available

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram of study selection.

Figure 2. Meta-analysis for treatment effect of hemofiltration on (A) mortality within 90 days, (B) ICU mortality, (C) in hospital mortality, (D) length of ICU stay, and (E) length of hospital stay.

Figure 3. Sensitivity analysis using leave-one-out approach for the treatment effect of hemofiltration (A) mortality within 90 days, (B) ICU mortality, and (C) in hospital mortality.

Figure S1. Quality assessment.

Table 1. Summary of basic characteristics of studies included in the for meta-analysis

Study	Study design	Number of patients	Treatment	Prescribed dose (mL/kg/h)	Delivered dose (mL/kg/h)	Duration (d)	Age (y)	Male (%)	Major cause of AKI	Sepsis	Oliguria	Mean APACHE II score
Joannes-Boyau (2013)	RCT	66	High-volume HF	70	65.6 (40–67.9)*	96 h	68 (58–77)*	68.0%	Sepsis	66 (100%)		
		71	Standard-volume HF	35	33.2 (28.7–33.6)*		70 (58–75)*	54.0%		71 (100%)		
Vesconi (2009)	Prospective	75	More-intensive	35	44.8 (9.4)	2 (1–3)*	61.01 (17.4)	58.1%		33 (40.5%)	36 (48.6%)	
		202	Less-intensive	21-34	26.9 (4.0)	4 (2–8)*	63.48 (15.9)	67.8%	Surgery	81 (40.1%)	84 (41.7%)	
		61	Less-intensive	20	15.4 (4.2)	3 (2–6)*	59.05 (19.0)	73.8%		19 (31.2%)	30 (49.5%)	
Zhang (2012)	RCT	141	EHVHF	85	87.54 (12.54)	9.38 (12. 06)	56.62 (16.38)	58.9%	Septic shock	72 (51.06%)		21.97
		139	HVHF	50	49.99 (9.65)	8.88 (10.79)	59.96 (18.81)	64.0%		69 (49.64%)		22.6
Bouman (2002)	RCT	35	EHV	72	48.2 (42.3–58.7)*	68.5 (28.0–140.8)*,†	68 (13)	60.0%	Cardiac surgery		35 (100%)	23.5
		35	ELV	24-36	20.1 (17.5–22.0)*	94.0 (53.0–181.5)*,†	70 (10)	57.0%			35 (100%)	21.7
		36	LLV	24-36	19.0 (16.6–21.2)*	69.5 (28.3–157.7)*,†	67 (13)	61.0%			30 (100%)	23.6
Tolwani (2008)	RCT	100	High Dosage	35	29	10.0 (9.8)	58 (16)	59.0%	Septic shock	54 (54%)	64 (64%)	26
		100	Standard Dosage	20	17	9.7 (11.3)	62 (15)	57.0%		54 (54%)	63 (63%)	26
Bellomo (2009)	RCT	722	Higher-Intensity CRRT	40	33.4 (12.8)	6.3 (8.7)	64.7(14.5)	65.7%	Sepsis	360 (49.9)	430 (59.6%)	102.5‡
		743	Lower-Intensity CRRT	25	22 (17.8)	5.9 (7.7)	64.4 (15.3)	63.5%		363 (48.9)	444 (59.8%)	102.3‡

Bousseke y (2008)	RCT	9	HVHF	65	62	7 (2–17)*	68 (58–74)*	78.0%	Sepsis	9 (100 %)	31
		10	LVHF	35	32	6 (2–14)*	72.5 (54–77)*	80.0%		10 (100%)	33.5
Ronco (2000)	RCT	146		20			61 (10)	55.5%		20 (14%)	22
		139		35			59 (9)	55.4%	Surgery	17 (12%)	24
		140		45			63 (12)	57.1%		15 (11%)	22

AKI, acute kidney injury; CRRT, continuous renal-replacement therapy; EHV, early high-volume hemofiltration; EHVHF, extra high-volume hemofiltration; ELV, early low-volume hemofiltration; HVHF, high-volume hemofiltration; LLV, late low-volume hemofiltration LVHF, low-volume hemofiltration; RCT, randomized controlled trial.,

*Data were presented by median and inter-quartile range (IQR), and by mean and standard deviation (SD) if not specified.

†Numbers were shown in hours.

‡Measured by APACHE III.

Table 2. Sensitivity-analysis for treatment effect on mortality according to different cut-off points of prescribed dose and delivered dose

	Number of studies included	Pooled odds ratio	Lower limit	Upper limit	Z-Value	P-Value
Prescribed dose						
(A) 90-day mortality						
50 mL/kg/h	2	0.97	0.66	1.43	-0.16	0.88
40 mL/kg/h	3	0.83	0.50	1.38	-0.71	0.48
30 mL/kg/h	2	0.73	0.39	1.38	-0.97	0.33
(B) ICU mortality						
50 mL/kg/h	1	1.20	0.58	2.47	0.50	0.62
40 mL/kg/h	2	1.04	0.85	1.28	0.37	0.72
30 mL/kg/h	3	1.13	0.92	1.38	1.18	0.24
(C) Hospital mortality						
50 mL/kg/h	2	1.11	0.75	1.65	0.53	0.60
40 mL/kg/h	2	1.02	0.71	1.45	0.08	0.94
30 mL/kg/h	2	0.98	0.73	1.31	-0.15	0.88
Delivered dose						
(A) 90-day mortality						
50 mL/kg/h	2	0.97	0.66	1.43	-0.16	0.88
40 mL/kg/h	1	1.24	0.63	2.43	0.63	0.53
30 mL/kg/h*	1	1.00	0.81	1.23	-0.03	0.97
(B) ICU mortality						
50 mL/kg/h	1	1.20	0.58	2.47	0.50	0.62
40 mL/kg/h	2	1.39	0.96	2.00	1.75	0.08
30 mL/kg/h	2	1.16	0.84	1.62	0.90	0.37

(C) Hospital mortality

50 mL/kg/h	1	0.99	0.61	1.61	-0.03	0.98
40 mL/kg/h	1	1.39	0.71	2.74	0.96	0.34
30 mL/kg/h	1	0.91	0.65	1.29	-0.52	0.60

*Ronco et al. (2000) did not provide information on delivered dose of continuous renal replacement therapy, and therefore was excluded.

Table 3. Meta-regression analysis for each outcome

Outcome	Intercept[a]	Slope[a]
Mortality within 90 days	-0.42 (0.19)	0.01 (0.004)
ICU mortality	0.31 (0.35)	-0.004 (0.01)
Hospital mortality	0.31 (0.34)	-0.01 (0.01)
Length of ICU stay	-2.89 (1.90)	0.03 (0.04)
Length of hospital stay	-1.74 (4.13)	0.034 (0.08)

[a]Presented as point estimate of coefficient and standard error.

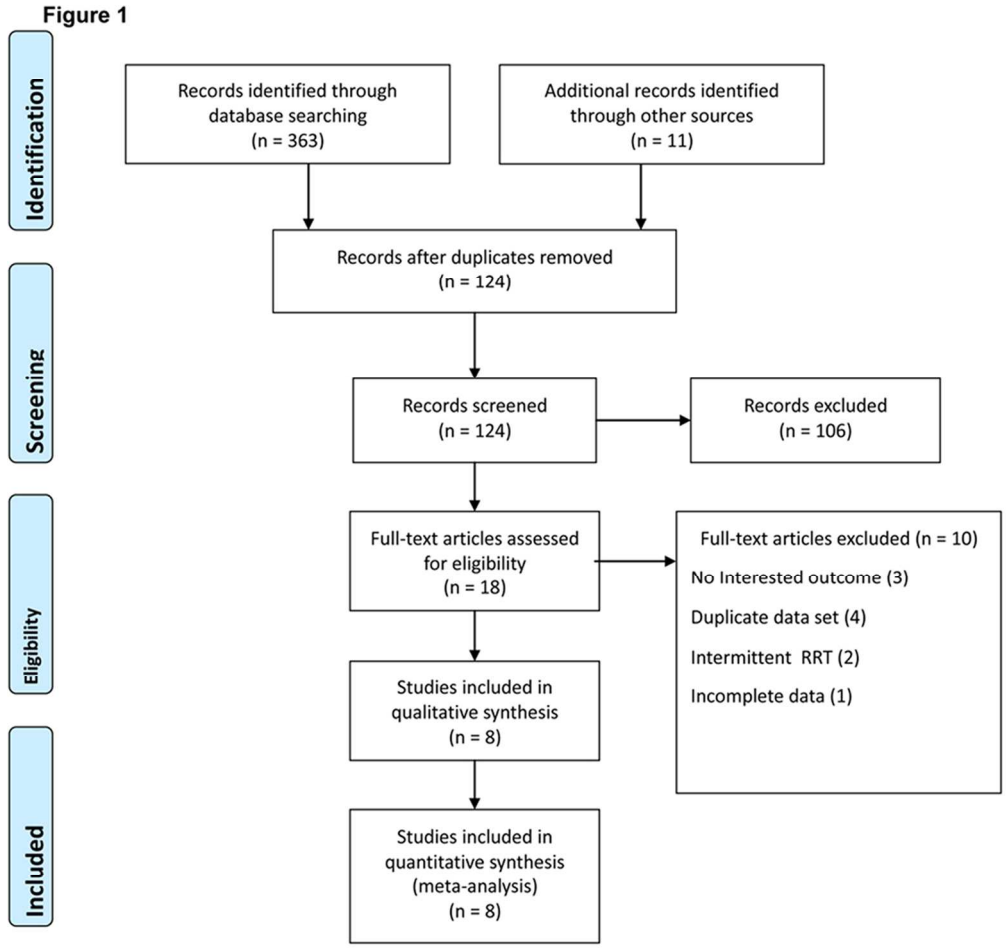
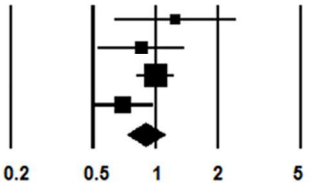


Figure 1

99x99mm (300 x 300 DPI)

(A) 90-day mortality

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	1.24	0.63	2.43	0.63	0.53
Zhang (2012)	0.85	0.53	1.38	-0.64	0.52
Bellomo (2009)	1.00	0.81	1.22	-0.03	0.97
Ronco (2000)	0.70	0.50	0.97	-2.12	0.03
Pooled	0.90	0.73	1.11	-1.00	0.32



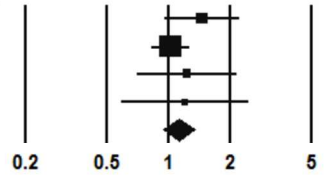
Heterogeneity test: Q = 4.10, P = 0.25, I^2 = 26.7%

Figure 2A

150x57mm (300 x 300 DPI)

(B) ICU mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Vesconi (2009)	1.46	0.95	2.22	1.74	0.08
Bellomo (2009)	1.03	0.83	1.27	0.23	0.82
Tolwani (2008)	1.23	0.70	2.15	0.71	0.47
Bouman (2002)	1.20	0.58	2.47	0.49	0.62
Pooled	1.12	0.94	1.34	1.26	0.21



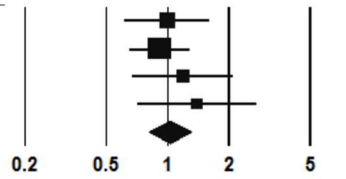
Heterogeneity test: Q = 2.24, P = 0.52, I^2 = 0%

Figure 2B

150x56mm (300 x 300 DPI)

(C) Hospital mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhang (2012)	0.99	0.61	1.61	-0.03	0.98
Bellomo (2009)	0.91	0.65	1.29	-0.52	0.60
Tolwani (2008)	1.19	0.67	2.10	0.58	0.56
Bouman (2002)	1.39	0.71	2.74	0.96	0.34
Pooled	1.02	0.81	1.30	0.20	0.84



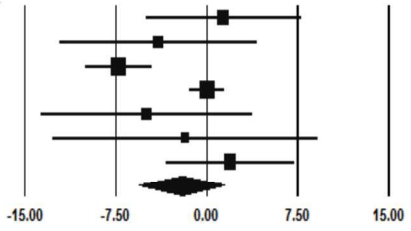
Heterogeneity test: Q = 1.49, P = 0.69, I^2 = 0%

Figure 2C

150x57mm (300 x 300 DPI)

(D) Length of ICU stay

Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	1.33	-5.08	7.74	0.41	0.68
Zhang (2012)	-4.01	-12.14	4.12	-0.97	0.33
Vesconi (2009)	-7.30	-10.00	-4.60	-5.29	0.00
Bellomo (2009)	0.00	-1.45	1.45	0.00	1.00
Tolwani (2008)	-5.00	-13.70	3.70	-1.13	0.26
Boussekey (2008)	-1.84	-12.77	9.09	-0.33	0.74
Bouman (2002)	1.91	-3.42	7.24	0.70	0.48
Pooled	-2.09	-5.64	1.45	-1.16	0.25



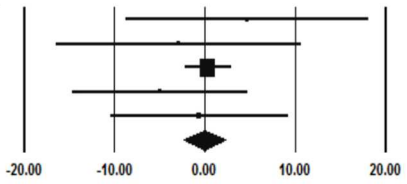
Heterogeneity test: Q = 25.10, P < 0.001, I^2 = 76.1%

Figure 2D

150x61mm (300 x 300 DPI)

(E) Length of hospital stay

Study name	Statistics for each study				
	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Joannes-Boyau (2013)	4.63	-8.84	18.10	0.67	0.50
Zhang (2012)	-2.94	-16.52	10.64	-0.42	0.67
Bellomo (2009)	0.30	-2.29	2.89	0.23	0.82
Tolwani (2008)	-5.00	-14.64	4.64	-1.02	0.31
Bouman (2002)	-0.67	-10.52	9.18	-0.13	0.89
Pooled	-0.03	-2.38	2.31	-0.03	0.98



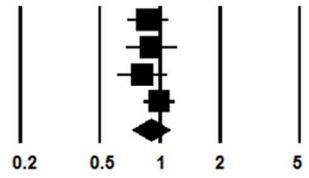
Heterogeneity test: Q = 1.74, P = 0.78, I^2 = 0%

Figure 2E

150x55mm (300 x 300 DPI)

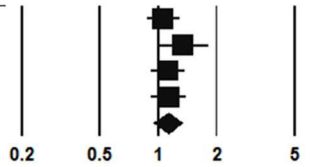
(A) 90-day mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Joannes-Boyau (2013)	0.867	0.686	1.096	-1.195	0.232	
Zhang (2012)	0.906	0.679	1.209	-0.672	0.502	
Bellomo (2009)	0.815	0.612	1.085	-1.403	0.161	
Ronco (2000)	0.991	0.825	1.189	-0.102	0.919	
Pooled	0.899	0.728	1.109	-0.996	0.319	



(B) ICU mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Vesconi (2009)	1.060	0.873	1.287	0.589	0.556	
Bellomo (2009)	1.336	0.984	1.815	1.854	0.064	
Tolwani (2008)	1.119	0.914	1.368	1.091	0.275	
Bouman (2002)	1.129	0.922	1.382	1.175	0.240	
Pooled	1.120	0.939	1.335	1.257	0.209	



(C) Hospital mortality

Study name	Statistics with study removed					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Zhang (2012)	1.035	0.790	1.356	0.249	0.803	
Bellomo (2009)	1.135	0.821	1.569	0.768	0.442	
Tolwani (2008)	0.995	0.768	1.289	-0.041	0.968	
Bouman (2002)	0.982	0.764	1.263	-0.139	0.889	
Pooled	1.025	0.809	1.297	0.203	0.839	

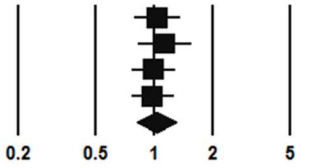


Figure 3

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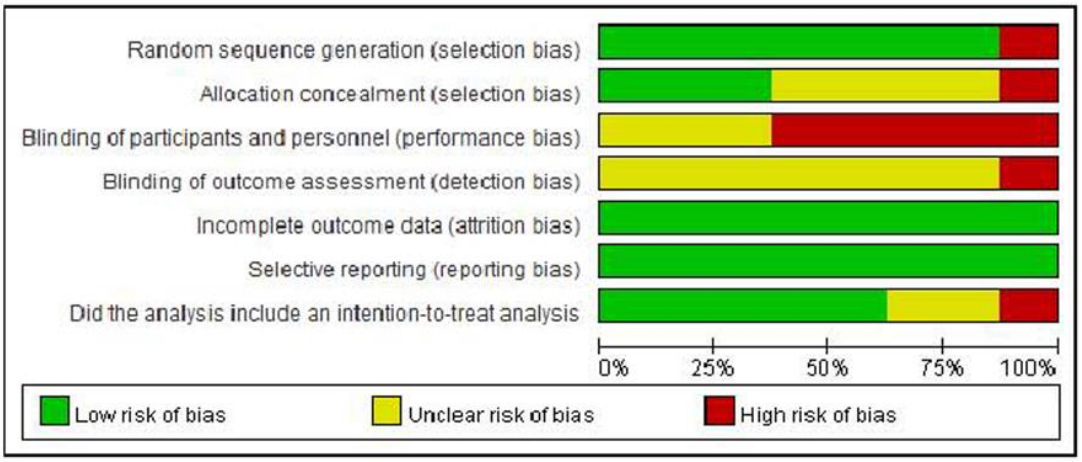
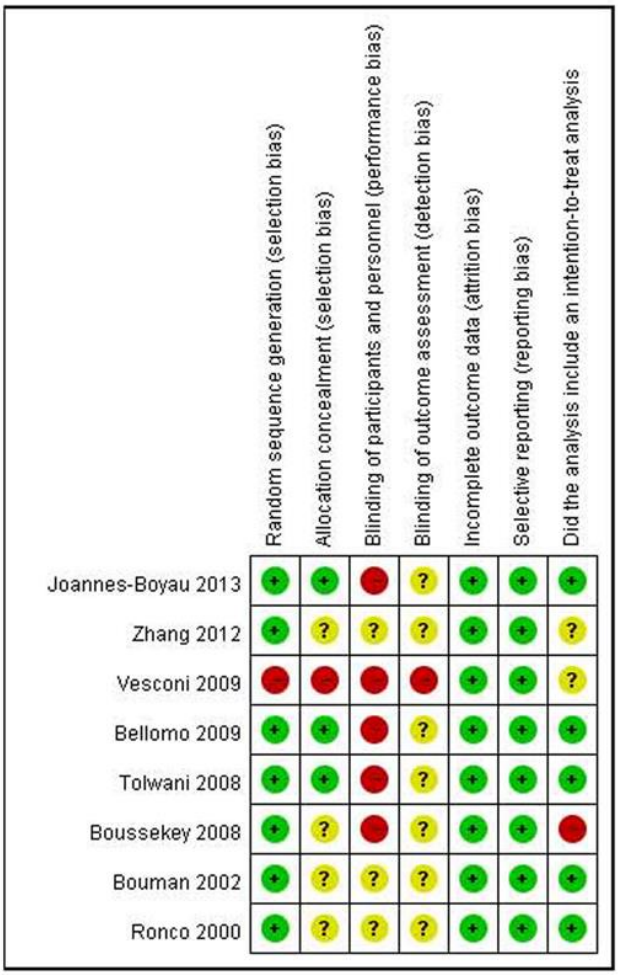
Figure S1

(A)


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)
Did the analysis include an intention-to-treat analysis
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

(B)


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)
Did the analysis include an intention-to-treat analysis
Joannes-Boyau 2013
Zhang 2012
Vesconi 2009
Bellomo 2009
Tolwani 2008
Boussekey 2008
Bouman 2002
Ronco 2000

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist