PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	High- vs. low-dose hemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis
AUTHORS	Li, Peng; Qu, Li-ping; Qi, Dong; Shen, Bo; Wang, Yi-mei; Xu, Jia-rui; Jiang, Wu-hua; Zhang, Hao; Ding, Xiao-qiang; Teng, Jie

VERSION 1 - REVIEW

REVIEWER	Achim Joerres Department of Medicine I, Nephrology, Transplantation & Medical Intensive Care, Klinikum Cologne-Merheim, Germany
REVIEW RETURNED	27-Oct-2016

GENERAL COMMENTS	Li and colleagues present an updated systematic review and meta-analysis of studies comparing the dose of continuous renal replacement therapy in patients with AKI. Comments: The question of optimal dose for CRRT in patients with AKI is an important and yet debated one. Thus, an updated metaanalysis of studies in this area is of considerable interest. There are, however, some important points to address: (i) The studies by Joannes-Boyau et al and Zhang et al specifically investigated patients with sepsis. The underlying hypotheses of these studies is that very high treatment volumes might remove pro-inflammatory mediators and thus contribute to improved survival of these patients. Moreover, the “low intensity” groups in these studies had higher or at least similar treatment volumes compared to the “high intensity” groups in the other included studies. This overlap, together with the possibility that the relationship between CRRT intensity and outcome rather resembles an inverted U-shaped curve (Kellum&Ronco, Nat Rev Nephrol 2010), in my view precludes meaningful conclusions if these studies are analyzed together. (ii) The title of this manuscript implies that the delivered dose of CRRT is analyzed, however, in truth the prescribed CRRT dose is entered in the calculations. From DoReMi (Vesconi et al) and other studies we know, however, that there is quite a gulf between prescribed and actually delivered CRRT dose even under the conditions of a controlled clinical trial. This further adds to the uncertainties mentioned under (i).

REVIEWER	Matthias Girndt Department of Internal Medicine II Martin-Luther-University Halle-Wittenberg Germany
REVIEW RETURNED	04-Nov-2016

GENERAL COMMENTS	Li and coworkers provide an updated meta-analysis on the question if high-intensity hemofiltration has benefit over standard hemofiltration in patients with acute kidney injury in the intensive care unit. The analysis is well performed and the manuscript is well written. Prior meta-analyses on this topic came to the conclusion that high-intensity CRRT is not superior to standard CRRT in terms of mortality. After the most recent meta-analysis (Ref #21) two more studies were published, each of them was negative with regard to the primary end-point. On those grounds the priority for a new meta-analysis might be questioned. Nevertheless, this analysis is very well done in terms of statistics and interpretation. Abstract: What was the null hypothesis of this analysis, that high-dose treatment puts the patient at higher risk of mortality (results section) or that high-dose treatment is beneficial (discussion section)? Introduction: The introduction is a little imprecise when introducing the research question. The comparison of hemofiltration vs. hemodialysis which is introduced in the second paragraph is not the topic studied here. Further, the third paragraph uses the term CRRT which may include both, hemodialysis and hemofiltration. Later on, this meta-analysis is very clearly focusing on hemofiltration as the only CRRT modality that is studied. Why confusing the reader in the first place? I'd also suggest to use high-dose vs. low-dose hemofiltration instead of the term "CRRT" since CRRT potentially includes further treatment modalities such as SLED, EDD. Introduction: P5, l 58: "better clearance", better in comparison to which kind of treatment? The authors should also consider to discuss also the large meta-analysis by Friedrich and coworkers, Crit Care 2012; 16:R146

REVIEWER	Brittany Lapin Assistant Staff Biostatistics Department of Quantitative Health Sciences Cleveland Clinic USA
REVIEW RETURNED	21-Nov-2016

GENERAL COMMENTS	Overall, this is an extensive review and meta-analysis of the current literature on this topic. The authors did an excellent job of critically appraising the existing studies and their conclusions. A couple issues: 1. A thorough proof-reading is necessary. 2. For inclusion in the meta-analysis, how was decision for inclusion made? Please specify how many reviewers had to agree on inclusion, and how data were extracted from the study. At least 2 reviewers should independently extract study data and discordant data should be solved by a consensus. 3. Was publication bias investigated? Funnel plots or Egger's regression test should be used to assess the potential risk of publication bias. Or this should at least be mentioned in the limitations.

	4. There are too many tables and figures. Consider removing Figure 4, Table 3, and possibly Figure 5.

REVIEWER	Swapnil Hiremath Ottawa Hospital Research Institute, Canada
REVIEW RETURNED	06-Dec-2016

GENERAL COMMENTS	Li and colleagues have conducted a meta-analysis to assess the benefit of hemofiltration dose and outcomes in acute kidney injury. This manuscript needs revision, as detailed below: Introduction - Convection removes middle molecular weight solute rather than high molecular weight solute, as stated in the introduction - some citation numbers appear in the middle of the text eg 'Hemodialysis removes solute by diffusion out of the bloodstream into the [8] dialysate using a concentration' - the rationale for choosing only hemofiltration is not clearly explained. though hypothesized to be superior, there is connflicting data on the superiority of convection alone (ie hemofiltration) over diffusion or a mix (eg CVVHDF) Methods: - Was an information specialist or libararian involved in designing or executing the literature search? - Why did the authors choose to include non-RCTs? - Page 7, line 45: Cochran Q and I-squared help for identifying heterogeneity, not study quality. Consider using tools such as the Cochrane risk of bias (Higgins et al http://www.bmj.com/content/343/bmj.d5928) - Why did the authors choose random-effects method? Except for one analysis, there is very little heterogeneity, and fixed effects would have been fine? - Was this review registered? (eg at PROSPERO) results - Page 9, 1st paragraph of results: some studies were excluded for using low or intermittent doses of CRRT? What was considered low or intermittent? This is not specified in the methods as an exclusion criterion - Metaanalysis: Suggest presenting summary OR first and then the heterogeneity stats. - These sentences are contradictory: 'Large heterogeneity was observed across the seven studies that reported data for length of hospital stay (Q=25.10, P = 0.002, I2 = 76.1%). No heterogeneity was observed for data regarding length of hospital stay (Q=1.74, P=0.784, I2=0%)." - The authors have used risk of bias tool, it seems, in results - but not attributed in methods - The univariate metaregression carried out is reasonable (on proportion of patients with sepsis at a study level) A more useful analysis would be subgroup analysis to see if the heterogeneity is resolved by examining different covariates

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Achim Joerres
Institution and Country: Department of Medicine I,
Nephrology, Transplantation & Medical Intensive Care, Klinikum Cologne-Merheim, Germany
Please state any competing interests: None declared

Please leave your comments for the authors below

Li and colleagues present an updated systematic review and meta-analysis of studies comparing the dose of continuous renal replacement therapy in patients with AKI.

Comments:
The question of optimal dose for CRRT in patients with AKI is an important and yet debated one. Thus, an updated metaanalysis of studies in this area is of considerable interest. There are, however, some important points to address:

(i) The studies by Joannes-Boyau et al and Zhang et al specifically investigated patients with sepsis. The underlying hypotheses of these studies is that very high treatment volumes might remove pro-inflammatory mediators and thus contribute to improved survival of these patients. Moreover, the “low intensity” groups in these studies had higher or at least similar treatment volumes compared to the “high intensity” groups in the other included studies. This overlap, together with the possibility that the relationship between CRRT intensity and outcome rather resembles an inverted U-shaped curve (Kellum&Ronco, Nat Rev Nephrol 2010), in my view precludes meaningful conclusions if these studies are analyzed together.

(ii) The title of this manuscript implies that the delivered dose of CRRT is analyzed, however, in truth the prescribed CRRT dose is entered in the calculations. From DoReMi (Vesconi et al) and other studies we know, however, that there is quite a gulf between prescribed and actually delivered CRRT dose even under the conditions of a controlled clinical trial. This further adds to the uncertainties mentioned under (i).
Response: Thank you for your comments and the important points you have raised.

We do realize that the variation in dosage (classification of ‘low intensity’ or ‘high intensity’) within each included study will cause high heterogeneity; and hence influence the results.

In order to address this problem, we performed a sensitivity analysis by stratifying studies with different prescribed doses of 30, 40, or 50 ml/kg/h (Table 2). Although we understand that there are still limitations to this method of analysis, we have attempted to minimize the heterogeneity.

In addition, we have added an analysis of the delivered dosage (instead of the prescribed dose) that was reported in each study. The results for the delivered dose and prescribed dose were similar; hence, we may conclude that at least for the included trials within this study, the delivered dose was comparable to the prescribed dose, and did not largely influence the results.

to address this study may serve as guidance for future research. The points regarding heterogeneity have also been discussed as limitations of the study.

Reviewer: 2
Reviewer Name: Matthias Girndt

Institution and Country: Department of Internal Medicine II, Martin-Luther-University Halle-Wittenberg, Germany
Please state any competing interests: None declared

Please leave your comments for the authors below

Li and coworkers provide an updated meta-analysis on the question if high-intensity hemofiltration has benefit over standard hemofiltration in patients with acute kidney injury in the intensive care unit. The analysis is well performed and the manuscript is well written. Prior meta-analyses on this topic came to the conclusion that high-intensity CRRT is not superior to standard CRRT in terms of mortality. After the most recent meta-analysis (Ref #21) two more studies were published, each of them was negative with regard to the primary end-point. On those grounds the priority for a new meta-analysis might be questioned. Nevertheless, this analysis is very well done in terms of statistics and interpretation.

Abstract: What was the null hypothesis of this analysis, that high-dose treatment puts the patient at higher risk of mortality (results section) or that high-dose treatment is beneficial (discussion section)?
Response:

The aim of this study was to evaluate the validity of prior systematic reviews and meta-analysis, such as the study by Negash et al in 2011, using more current clinical data.

We hypothesized that high-dose treatments do not necessarily have a higher risk of mortality.

Although similar meta-analysis have been performed in the past, there are still conflicting results in the literature regarding outcomes of high- vs. low-dose treatment. Thus, any additional information may help to clarify issues regarding the dose of RRT.

The above hypothesis has been stated in the manuscript.

Introduction: The introduction is a little imprecise when introducing the research question. The comparison of hemofiltration vs. hemodialysis which is introduced in the second paragraph is not the topic studied here. Further, the third paragraph uses the term CRRT which may include both, hemodialysis and hemofiltration. Later on, this meta-analysis is very clearly focusing on hemofiltration as the only CRRT modality that is studied. Why confusing the reader in the first place? I'd also suggest to use high-dose vs. low-dose hemofiltration instead of the term "CRRT" since CRRT potentially includes further treatment modalities such as SLED, EDD.
Response:
Thank you for the points you have raised. We have revised the title and the text of the manuscript to indicate that this study is focused on hemofiltration and not other methods of CRRT.

Introduction: P5, l 58: "better clearance", better in comparison to which kind of treatment?
Response:
We have revised the sentence as follows: "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]"

The authors should also consider to discuss also the large meta-analysis by Friedrich and coworkers, Crit Care 2012; 16:R146
Response:

Thank you for pointing out our error. We have discussed the meta-analysis by Friedrich et al. (2012) in the revised manuscript.

Reviewer: 3
Reviewer Name: Brittany Lapin
Institution and Country: Assistant Staff Biostatistics, Department of Quantitative Health Sciences, Cleveland Clinic, USA
Please state any competing interests: None declared

Please leave your comments for the authors below

Overall, this is an extensive review and meta-analysis of the current literature on this topic. The authors did an excellent job of critically appraising the existing studies and their conclusions. A couple issues:

1. A thorough proof-reading is necessary.
Response:
The manuscript has been revised and edited by a native English speaking professional medical writer.

2. For inclusion in the meta-analysis, how was decision for inclusion made? Please specify how many reviewers had to agree on inclusion, and how data were extracted from the study. At least 2 reviewers should independently extract study data and discordant data should be solved by a consensus.
Response:
We have clarified the methods to more specifically state how the studies were reviewed, data were extracted, and conflicts were resolved.

3. Was publication bias investigated? Funnel plots or Egger's regression test should be used to assess the potential risk of publication bias. Or this should at least be mentioned in the limitations.
Response:
Publication bias assessment was not performed due to limited number of included studies; 10 or more studies are necessary to assess publication bias. We have added this information and the supporting reference below to the manuscript.

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J,Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011 Jul 22;343:d4002.

3. There are too many tables and figures. Consider removing Figure 4, Table 3, and possibly Figure 5.
Response:
The numbers of tables and figures have been reduced, and some information has been included as supplemental material.

Reviewer: 4
Reviewer Name: Swapnil Hiremath
Institution and Country: Ottawa Hospital Research Institute, Canada

Please state any competing interests: None declared

Please leave your comments for the authors below

Li and colleagues have conducted a meta-analysis to assess the benefit of hemofiltration dose and outcomes in acute kidney injury. This manuscript needs revision, as detailed below:

Introduction
- Convection removes middle molecular weight solute rather than high molecular weight solute, as stated in the introduction
- some citation numbers appear in the middle of the text eg 'Hemodialysis removes solute by diffusion out of the bloodstream into the [8] dialysate using a concentration'
Response:
The above have been corrected, and the manuscript has been revised and edited by a native English speaking professional medical writer.

- the rationale for choosing only hemofiltration is not clearly explained. though hypothesized to be superior, there is connflicting data on the superiority of convection alone (ie hemofiltration) over diffusion or a mix (eg CVVHDF)
Response:

The intention of our meta-analysis was to examine the risks and benefits of using different doses of renal replacement therapy. During our literature search, we included all modalities of CRRT, regardless of hemofiltration or hemodialysis.

However, the search results 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.

We have discussed this point in the discussion of the limitations of the study.

Methods:
- Was an information specialist or libararian involved in designing or executing the literature search?
Response:
No specialist or librarian was involved in designing or executing the literature search. The literature search was performed by authors of the study.

- Why did the authors choose to include non-RCTs?
Response:
Although RCTs provides the best level of evidence with respect to any scientific research, we believe that prospective and retrospective studies still have value, especially in terms of critically ill patients with acute kidney injury.

Due to ethical reasons, in practice RCTs are not always possible. However, well designed non-randomized trials may also provide a high level of evidence that assists in answering clinical questions.

- Page 7, line 45: Cochran Q and I-squared help for identifying heterogeneity, not study quality. Consider using tools such as the Cochrane risk of bias (Higgins et al Response:
Please accept our apology for the error in translation. The Cochrane Risk of Bias tool was used to assess study quality. This has been corrected in the manuscript.

- Why did the authors choose random-effects method? Except for one analysis, there is very little heterogeneity, and fixed effects would have been fine?
Response:
Random-effect models were used to incorporate between-study variation where there exists unexplained heterogeneity across studies. In addition, a random-effects model gives small studies more weight than a fixed-effects analysis.

Furthermore, when heterogeneity exists, the confidence interval in random-effects analysis will be wider than if a fixed-effects analysis was performed (i.e., when I2 > 0), yielding a more conservative result.

- Was this review registered? (eg at PROSPERO)
Response:
The study is registered at http://www.researchregistry.com/
The registration number is reviewregistry211. We have added this information to the manuscript.

results
- Page 9, 1st paragraph of results: some studies were excluded for using low or intermittent doses of CRRT? What was considered low or intermittent? This is not specified in the methods as an exclusion criterion
Response:
Please accept our apology. This was an error of translation. The excluded studies were studies that used intermittent renal replacement therapies of different doses. This has been corrected.

- Metaanalysis: Suggest presenting summary OR first and then the heterogeneity stats.
- These sentences are contradictory: 'Large heterogeneity was observed across the seven studies that reported data for length of hospital stay (Q=25.10, P = 0.002, I2 = 76.1%). No heterogeneity was observed for data regarding length of hospital stay (Q=1.74, P=0.784, I2=0%)."
- The authors have used risk of bias tool, it seems, in results - but not attributed in methods
- The univariate metaregression carried out is reasonable (on proportion of patients with sepsis at a study level)

Response:
The results have been edited to resolve any discrepancies that were present, and presented in the order you have indicated.

The Cochrane Risk of Bias tool is discussed and referenced in the methods section.

A more useful analysis would be subgroup analysis to see if the heterogeneity is resolved by examining different covariates
Response:
We completely agree that a subgroup analysis of different covariates, such as according to renal function, would aid in the analysis. However, due to limited availability of raw data, very few variables can be investigated.

However, the study population that was included in this analysis were critically ill patients, and shared similar baseline risks.

We have added APACHE II/III scores to Table 1. The scores were reported in 6 of the eight studies, and mean scores were similar between the groups included in the individual studies, indicating that the groups compared in the individual studies were similar with respect to disease severity.

We have added the information regarding APACHE scores to the manuscript.

VERSION 2 – REVIEW

REVIEWER	Achim Joerres Department of Medicine I Nephrology, Transplantation & Medical Intensive Care, Klinikum Cologne-Merheim Cologne, Germany
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	I have no further comments to the authors

REVIEWER	Brittany Lapin Cleveland Clinic, USA
REVIEW RETURNED	28-Feb-2017

GENERAL COMMENTS	This revision is much improved and addresses all of my concerns. Thank you!

REVIEWER	Swapnil Hiremath Ottawa Hospital Research Institute
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	The authors have addressed most of the issues raised. - registration: This seems to have been done retro-actively on feb 17th 2017 (http://www.researchregistry.com/browse-the-registry.html#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/58a555312682bdfb48167513/) based on our request. This is somewhat unsettling - it would be more honest to say that the SR was not registered. - Suggest rounding down to 2 decimals for ease of reading (or per BMJ open style) Introduction: - Statement in Introduction 'Hemofiltration is superior to hemodialysis in patients with AKI as it is believed that is can remove the toxic mediators of sepsis and inflammation.' is inaccurate: hemofiltration is not superior, it is believed to be superior Results: - The authors state 'The doses used also varied, ranging from 20 to 85 mL/kg/h.' It would be more useful to state: "The dose used in low dose ranged from 'xx to xx' and in high dose from yy to yy ' - Meta-analysis. The summary results are not stated in the text - refer to figure/table is not useful. Please state summary OR (95%CI) in text.

	Conclusion: 'However, additional well-designed studies are necessary to further investigate what is the optimal CRRT for critically ill patients with AKI." This is somewhat open-ended. What study would one propose to do? Do the authors really think there is a potential benefit for high dose CRRT? Based on the SR, could the authors run a sample size estimation?

VERSION 2 – AUTHOR RESPONSE

Responses to reviewer comments
Reviewer Name
Achim Joerres

Institution and Country
Department of Medicine I
Nephrology, Transplantation & Medical Intensive Care, Klinikum Cologne-Merheim
Cologne, Germany

Please state any competing interests or state 'None declared':
none declared

Please leave your comments for the authors below
I have no further comments to the authors

Reviewer: 4

Reviewer Name
Swapnil Hiremath

Institution and Country
Ottawa Hospital Research Institute

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
The authors have addressed most of the issues raised.

- registration: This seems to have been done retro-actively on feb 17th 2017 (http://www.researchregistry.com/browse-the-registry.html#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/58a555312682bdfb48167513/) based on our request. This is somewhat unsettling - it would be more honest to say that the SR was not registered.

Response: We have changed the explanation of registration as follows: "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."

- Suggest rounding down to 2 decimals for ease of reading (or per BMJ open style)
Response: Data have been rounded to 2 decimal places.

Introduction:
- Statement in Introduction 'Hemofiltration is superior to hemodialysis in patients with AKI as it is believed that is can remove the toxic mediators of sepsis and inflammation.' is inaccurate: hemofiltration is not superior, it is believed to be superior
Response: We have revised the sentence as follows: “ 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.”

Results:
- The authors state 'The doses used also varied, ranging from 20 to 85 mL/kg/h.' It would be more useful to state: "The dose used in low dose ranged from 'xx to xx' and in high dose from yy to yy '
Response: We have revised the sentence as follows: “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. The summary results are not stated in the text - refer to figure/table is not useful. Please state summary OR (95%CI) in text.
Response: The reporting of data in the text has been corrected.

Conclusion:
'However, additional well-designed studies are necessary to further investigate what is the optimal CRRT for critically ill patients with AKI." This is somewhat open-ended. What study would one propose to do? Do the authors really think there is a potential benefit for high dose CRRT? Based on the SR, could the authors run a sample size estimation?

Response: Thank you for your comment. We agree that the statement is contradictory as the current results indicated that high-dose CRRT had no survival benefit comparing to low-dose (even with the lowest cutoff of 30 mL/kg/h). We have thus deleted the sentence.

Reviewer: 3

Reviewer Name
Brittany Lapin

Institution and Country
Cleveland Clinic, USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
This revision is much improved and addresses all of my concerns. Thank you!