Author’s response to reviews

Title: A comparison of early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials

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RESPONSE TO REVIEWERS

Lili Chan (Reviewer 1): Overall comments:

This paper was well written and addresses an important clinical question regarding "early" vs "late" start RRT for AKI. In this systematic review and meta-analysis, the authors do not find a significant benefit to early or late start HD, and notes that there is significant heterogeneity. This systematic review and meta-analysis is done appropriately, with appropriate consideration of statistical method especially with regard to heterogeneity and random effects. They also appropriate discuss the limitations to their analysis.

Answer: We appreciate the comments on our study.
Major issues:

1. The authors notes that prior systematic reviews and meta-analysis have included low quality studies. However, there have many at least one that I have found that looked at RCT’s only, which included both the AKIKI and ELIANE trial.


Answer: Thanks to the reviewer and we fully agree. Several meta-analyses have been published regarding the optimal timing of RRT initiation that achieved conflicting conclusion. The paucity of RCTs involved in the meta-analysis precluded the establishment of definitive conclusions because non-RCTs may exaggerate the magnitude of the effect due to intrinsic and external factors. Recently, two well-designed RCTs were issued to evaluate the outcome of different strategies for RRT. Whatever, these findings added further uncertainty about the efficacy of “early” RRT in critically ill patients.

In the meta-analysis conducted by Xu Y et al, it included both the AKIKI and ELAIN trial. However, three RCTs were not included in the study (1-3), which were well done and were published in high level peer-reviewed journals (ATS, CCM, AJRCCM). Therefore, we think the conclusion of our study is more convincible.

REFERENCES


2. I am curious as to why the authors utilized these three databases only. Many often use Medline and GoogleScholar. Also there is the potential for abstracts/posters to have
additional RCT data that many not be available on these databases as they are not published in journals yet. Did the authors attempt to find non-traditional publications?

Answer: We screened PubMed, EMBASE and Cochrane databases because we aimed to enroll RCTs only in this meta-analysis. Thanks to the reviewer’s advice, we have attempted to search GoogleScholar and clinicaltrials.gov and have found several ongoing trials addressing the optimal timing of RRT initiation in AKI. However, no more results from these trials were reported.

Minor issues:

1. Page 6 Line 58, "if sufficient trials" can the authors please describe what was considered sufficient?

Answer: We are very sorry for the inaccurate expression. In the meta-analysis, sensitivity analyses were conducted by excluding or subgrouping studies to reduce the potential confounding effects, including patient population, RRT modality, study design, study sample size, duration of follow-up, urine output and creatinine. According to your comment, we have revised it in this version.

2. Page 6 Line 54: here they state that ethics board approval was not needed, however later on Page 18, they declare that this study was approved by the ethics board.

Answer: Thanks to the reviewer. All the studies should be under medical ethics review in principle in Zhongshan hospital, Fudan University. However, neither ethics board approval nor patient consent was required due to the nature of a systematic review. It has been revised in the new version.

3. Tables 2 and 3: consider grouping by criteria instead of year, as in all those with urine output together, and those with BUN together

Answer: Thanks to the reviewer’s advice. In Table 2, we listed the the definitions of “early” and “late” RRTs in the enrolled studies. The definitions of “early” and “late” RRT in these studies were generally based on urine output (UO), serum creatinine (SCr) levels or blood urea nitrogen (BUN) levels. However, different combinations of the markers were used in these studies. For example, UO+Scr, SCr+BUN, UO only and Scr only…… More even, the definitions of early RRT criteria in two studies did not include any of the markers above (1-2). Due to huge diversity on criteria of “early” RRT, we found it was difficult to group the studies depending on the reviewer’s suggestion.
REFERENCES


4. Forrest plots: some are blue and some are green boxes.

Answer: Thanks to the reviewer’s advice. The categorical variables (eg. Mortality, Figure 2) were showed as blue boxes and quantitative variables (eg. ICU LOS, Figure 3) were showed as green boxes in the forest plots. This is the system default in the RevMan 5.3 (Cochrane IMS, Oxford, UK). Actually, it is not necessary to distinguish these two types of variables by using different colors in the publication.

Kinsuk Chauhan, M.D., M.P.H. (Reviewer 2): Comments to the Author:

1. This is a well-constructed paper that shows comparison of early versus late initiation of RRT for AKI in critically ill patients. Overall a good approach to combine the results from various studies and try to reduce level of heterogeneity. The manuscript is well written and objectives were clearly stated.

Answer: We appreciate the comments on our study.

Some specific areas to attend to are noted below:

1. The authors have provided all possible keywords in the search strategy but needs to add a few more points, for example use of or/and/exp or use of ti, ab, etc. in the search string. Author can include search string used in different databases as a supplementary material.

Answer: Thanks to the reviewer’s advice. The search strategy terms and results were submitted as a supplementary material in the revised version.
2. Author should provide figure legends and titles of forest plots on top of each plots for easy understandability. Also, it would be interesting to see forest plot by RRT modality and by study centers for primary outcome.

Answer: Thanks to the reviewer’s advice. It is worthy mentioning that the figures and figure legends were required to submit separately via the submission system. The figure legend will be provided on the bottom of each forest plot in the formal publication.

The forest plot for RRT modality (Figure 3) and study centers (Figure 4) have been added in the revised version.

3. Address for possible confounders related to study outcome, which were considered (or not) in different trials (such as, possible post-surgical complications, presence of severe comorbid conditions which could have impact on mortality) in the limitation section.

Answer: The suggestion is of great value, which we fully agree. We have addressed these possible confounders in the limitation section (marked red).

4. Based on results from meta-analysis, include what would be an appropriate sample size of for a future trial to get the conclusive effect of early vs late RRT on mortality.

Answer: This is a very good question! If based on the mortality rate of Early RRT (40.87%, 338/827) and Late RRT(42.52%, 334/809) (Figure 2), a sample size of 26318 would be an appropriate sample size to have a power of 80% at 5% level of significance in the PASS software.

5. Consider including a point about generalizability of the results in the discussion section.

Answer: The suggestion is of great value. Aforementioned, there is no established evidence of the association between timing of RRT initiation and outcomes. Due to the relatively high heterogeneity among enrolled studies, the conclusion of the meta-analysis should be interpreted with great caution. Although we could not reach the definite conclusion in our meta-analysis, we raise several suggestions for upcoming studies: (1) enrolled patients might be in a specified population, such as sepsis or post cardiovascular surgery, avoiding mixed populations; (2) using a unified definition of the timing of early and late RRT could facilitate reaching reliable conclusions; and (3) the endpoint outcome of studies and choice of modalities of RRT should also be uniform if possible. (marked red in the revised version).