Author’s response to reviews

Title: Early initiation of renal replacement therapy in critically ill patients: a meta-analysis of randomized clinical trials

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Author’s response to reviews:

Dear. Dr. Zaouter,

it is with great pleasure that we resubmit our edited manuscript, “Early initiation of renal replacement therapy in critically ill patients: a meta-analysis of randomized clinical trials”, for consideration of publication in BMC Anesthesiology.

We appreciate the excellent input of the expert reviewers. In addressing the extensive comments, we spent many hours heavily editing the manuscript, and feel that the paper is improved.

All the authors have reviewed the paper and have approved of its resubmission. None of the data are submitted elsewhere for consideration.

As the Editors and expert reviewers will see, we have taken great pains to address all comments. We hope these efforts have resulted in a manuscript viewed worthy of the high standard of BMC Anesthesiology.

With best wishes,

Dr Laura Pasin
Technical Comments:

Editor Comments:

I would like to congratulate the authors for their interesting work. However, as outlined below there several points that should be addressed. My concern, is that there are no new findings even if new trials have been included in the analysis. Therefore, the author should address this issue more in detail in their discussion. Is it because of the definition of "early" vs. "late /standard" RRT strategies?

We appreciate the Editor’s supportive comments. We totally agree with the Editor concerns regarding the lack of new findings in our study.

Given these thoughts, we have modified the text to emphasize this important shortcoming. The discussion section now reads:

…….” Although our meta-analysis includes all the randomized clinical trials ever published on early vs late RRT and two large, recent, high-quality RCTs, the optimal timing of initiating RRT remains unclear. Actually, we couldn’t add great new findings to previous published meta-analyses. A reasonable explanation for this is that our study is still underpowered for mortality. Moreover, the analyzed studies were conducted over a wide range of time, during which the management of AKI patients has greatly changed. In fact, in the last decade the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline contributed to standardize AKI treatment. This means that the more recent studies published after 2010 failed to show a significant survival benefit from early RRT treatment, while a reduction in mortality was shown by older studies. Initiation of RRT, to some extent, depends on creatinine level and urine output, namely, the KDIGO criteria. Therefore, one of the main limitations of our meta-analysis and of all the performed and ongoing trials is the lack of definition of “early” versus “late” criteria, that varied among the included studies and may have led to great differences in the requirements for RRT and their therapeutic impact. Larger, well conducted RCTs should be performed to further clarify this issue. Actually, there is another ongoing RCT that will probably provide additional informations on the optimal timing of starting RRT in critically ill patients admitted to general ICU (STARRT-AKI, NCT02568722). Unfortunately, given the previous reported limitations, this trial will not probably allow to draw definitive conclusions on the optimal timing of starting RRT in critically ill patients.”
We hope the Editor recognizes the efforts we have made to address his concerns.

Finally, the new findings of the more recent studies should be more precise. Could you please be more specific in that matter?

We appreciate the Editor identifying this important information missing from our manuscript. Introduction section now reads:

“Recently, a large, high-quality randomized clinical trial (RCT), the IDEAL-ICU trial was published in NEJM. [12] In this multicenter trial, 488 adults with septic shock and severe AKI were randomized to receive RRT within 12 hours (early strategy) of documented failure stage or after a delay of 48 hours (late strategy). Nearly all patients in the early-strategy group received RRT while approximately 30% of patients in the delayed-strategy group did not receive RRT since they had spontaneous recovery of renal function. The IDEAL-ICU trial was stopped early for futility. The primary outcome of mortality at 90 days did not differ between patients who received early versus late initiation of RRT (58% vs. 54%; P=0.38). Furthermore, no benefits were seen from early initiation of RRT in secondary outcomes. Results of previous larger studies were conflicting. In fact, one major trial (ELAIN) showed a 90-day mortality benefit, while another (AKIKI) did not show a benefit at 60 days. The ELAIN trial was smaller, conducted almost exclusively in postoperative AKI patients, and the difference in timing between early versus late initiation of RRT was less than 24 hours.”

BMC Anesthesiology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Demetrio Pittarello (Reviewer 1): It is a well-structured work that highlights the early initiation of RRT vs the RRT standard.
We thank the reviewer for his supportive comments.

Several previous systematic reviews have compared early vs standard RRT in different clinical settings (cardiac surgery, ICU) and by inclusion of studies with different designs (cohort studies and RCTs).

Early initiation of RRT may provide better control of fluid and electrolyte balance, superior acid-base homeostasis, increased removal of uremic waste, and prevention of subsequent complications attributable to AKI. Furthermore, early RRT could potentially limit the kidney-specific and remote organ injuries that result from fluid overload, electrolyte imbalance, and systemic inflammation. However, early RRT may also increase the risk of hemodynamic instability, anticoagulation-induced bleeding, blood-stream infection, and inflammatory or oxidative stress due to the bioincompatibility of the dialyzer membranes. Standard initiation of RRT may allow more time for hemodynamic optimization prior to RRT and may prevent the need for RRT and its associated complications.

Studies analyzed were conducted over a wide range of time, during which the management of AKI patients has changed a lot. In the past decade the KDIGO Clinical Practice Guideline contributed to standardize AKI treatment. This means that more recent studies published after 2010 failed to show a significant survival benefit from early RRT treatment, while a reduction in mortality was shown by older studies. In other words, although many studies have investigated the optimal timing for initiation of RRT, the results remain controversial. Initiation of RRT, to some extent, depends on SCr level and urine output, namely, the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. So I think that the question remains the definition of early criteria, that varied among the included studies, and this may have led to differences in the requirements for RRT and their therapeutic impact. This is the reason why, despite the conclusions obtained, is necessary to perform large, multicentered RCTs to confirm the results of this meta-analysis. Beyond these considerations I consider valid and important the study that provides a further contribution to the attempt to answer the question.

We appreciate these comments and we thank the reviewer for this challenging suggestion, which has strengthened our argument. Given these thoughts, we have modified the text to emphasize this important shortcoming. The discussion section now reads:

…….” Although our meta-analysis includes all the randomized clinical trials ever published on early vs late RRT and two large, recent, high-quality RCTs, the optimal timing of initiating RRT remains unclear. Actually, we couldn’t add great new findings to previous published meta-
analyses. A reasonable explanation for this is that our study is still underpowered for mortality. Moreover, the analyzed studies were conducted over a wide range of time, during which the management of AKI patients has greatly changed. In fact, in the last decade the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline contributed to standardize AKI treatment. This means that the more recent studies published after 2010 failed to show a significant survival benefit from early RRT treatment, while a reduction in mortality was shown by older studies. Initiation of RRT, to some extent, depends on creatinine level and urine output, namely, the KDIGO criteria. Therefore, one of the main limitations of our meta-analysis and of all the performed and ongoing trials is the lack of definition of “early” versus “late” criteria, that varied among the included studies and may have led to great differences in the requirements for RRT and their therapeutic impact. Larger, well conducted RCTs should be performed to further clarify this issue. Actually, there is another ongoing RCT that will probably provide additional informations on the optimal timing of starting RRT in critically ill patients admitted to general ICU (STARRT-AKI, NCT02568722). Unfortunately, given the previous reported limitations, this trial will not probably allow to draw definitive conclusions on the optimal timing of starting RRT in critically ill patients.

Fabian Dusse, MD, MHBA (Reviewer 2): Pasin and colleagues performed a meta-analysis including 10 RCTs with the aim to estimate the benefit of early RRT initiation.

major comments:

1. The heterogeneity among the included studies in the definition of "early" vs. "late /standard" makes it difficult to compare the respective results. Patients who are assigned to the "late group" in one study (<12h) may be assigned to the "early group" in another study (<48h).

We totally agree with the Reviewer concerns regarding the high heterogeneity among the definition of “early” vs “late/standard” initiation of RRT.

Given these thoughts, we have modified the text to emphasize this important shortcoming. The discussion section now reads:

……” Although our meta-analysis includes all the randomized clinical trials ever published on early vs late RRT and two large, recent, high-quality RCTs, the optimal timing of initiating RRT remains unclear. Actually, we couldn’t add great new findings to previous published meta-analyses. A reasonable explanation for this is that our study is still underpowered for mortality.
Moreover, the analyzed studies were conducted over a wide range of time, during which the management of AKI patients has greatly changed. In fact, in the last decade the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline contributed to standardize AKI treatment. This means that the more recent studies published after 2010 failed to show a significant survival benefit from early RRT treatment, while a reduction in mortality was shown by older studies. Initiation of RRT, to some extent, depends on creatinine level and urine output, namely, the KDIGO criteria. Therefore, one of the main limitations of our meta-analysis and of all the performed and ongoing trials is the lack of definition of “early” versus “late” criteria, that varied among the included studies and may have led to great differences in the requirements for RRT and their therapeutic impact. Larger, well conducted RCTs should be performed to further clarify this issue. Actually, there is another ongoing RCT that will probably provide additional informations on the optimal timing of starting RRT in critically ill patients admitted to general ICU (STARRT-AKI, NCT02568722). Unfortunately, given the previous reported limitations, this trial will not probably allow to draw definitive conclusions on the optimal timing of starting RRT in critically ill patients.

We hope the Reviewer recognizes the efforts we have made to address his concerns.

2. The "Standard indication" for RRT is not defined.

We appreciate the reviewer identifying this important information missing from our manuscript.

We added standard indications for RRT of all the included studies, as per author definition. Please see Table 1 for details.

3. Several meta-analysis have been published in the recent years that address the same question. Although the studies included differ, the results and conclusions are comparable. It is not clearly stated, what the new findings of the current study are.

We totally agree with the Reviewer concerns regarding the lack of new findings in our study. Given these thoughts, we have modified the text to emphasize this important shortcoming. The discussion section now reads:

……..” Although our meta-analysis includes all the randomized clinical trials ever published on early vs late RRT and two large, recent, high-quality RCTs, the optimal timing of initiating RRT remains unclear. Actually, we couldn’t add great new findings to previous published meta-analyses. A reasonable explanation for this is that our study is still underpowered for mortality.
Moreover, the analyzed studies were conducted over a wide range of time, during which the management of AKI patients has greatly changed. In fact, in the last decade the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline contributed to standardize AKI treatment. This means that the more recent studies published after 2010 failed to show a significant survival benefit from early RRT treatment, while a reduction in mortality was shown by older studies. Initiation of RRT, to some extent, depends on creatinine level and urine output, namely, the KDIGO criteria. Therefore, one of the main limitations of our meta-analysis and of all the performed and ongoing trials is the lack of definition of “early” versus “late” criteria, that varied among the included studies and may have led to great differences in the requirements for RRT and their therapeutic impact. Larger, well conducted RCTs should be performed to further clarify this issue. Actually, there is another ongoing RCT that will probably provide additional informations on the optimal timing of starting RRT in critically ill patients admitted to general ICU (STARRT-AKI, NCT02568722). Unfortunately, given the previous reported limitations, this trial will not probably allow to draw definitive conclusions on the optimal timing of starting RRT in critically ill patients.

We hope the Reviewer recognizes the efforts we have made to address his concerns.

4. No legends are provided for the figures. This makes it difficult to put them into the context, especially for fig. 2 +3.

Again, we would like to thank the reviewer for identifying this missing information in the figure. Figure legends have now been added and the text now reads:

Figure legends

Figure 1: flow-chart for study selection

Figure 2: Forest plot for mortality

Figure 3: Forest plot for survival with dependence on RRT

minor comments

some typing errors, e.g.

p9 L47 "me"
We thank the Reviewer for this insightful comment. The text now reads:

“to mortality and ICU and hospital length of stay”