Peer Review File

Article information: https://dx.doi.org/10.21037/tau-23-146

Reviewer A

In this study, the authors have retrospectively evaluated patients with heart failure who received CRRT and divided them into “early” and “delayed”, and then evaluated clinical outcomes. I think the idea of looking at early vs late CRRT initiation in heart failure patients has the potential to make a contribution to the literature, since this group not well-studied with regards to CRRT initiation. However, there are some major flaws present that limit my excitement for the paper.

1. There are major issues with the way the groups are defined.
a. The “delayed” group actually initiated CRRT earlier than the “early” group. The interval from AKI diagnosis to RRT initiation was 8 hours for the “delayed” group, vs 12 hours for the “early” group. The patients seem to be classified more by stage of AKI and degree of fluid overload than by time to CRRT initiation, which is a major flaw.
b. Patients with emergent indications for dialysis are counted in the “delayed” group, and the rationale for this decision is not explained. The authors may be assuming that these patients must have been “delayed” in order for there to be sufficient time for emergent indications to develop. However, the gap of only 8 hours from AKI development to initiation must mean that the group of patients with emergent indications was either small, or that this assumption was invalid.
c. The grouping by degree of volume overload also seemed to have problems, as the degree of fluid overload was non-significantly higher in the “early” start than the “delayed” start groups, even though FOP was a reason to classify patients in the “delayed” group (along with also having Stage 3 AKI or emergent indications for HD).
d. If there are no differences in time to initiation, and no differences in volume overload, what is left essentially is comparing CRRT in patients with mostly Stage 3 AKI and emergent indications for HD vs those with mostly Stage 1-2 AKI without emergent indications for AKI. It is actually surprising given the way this study was set up that the early group was not favored, which I suspect is a power issue.

Reply 1: Thanks for taking your time to review this manuscript. I really appreciate all your comments and suggestions!
a. We agree that the interval from AKI diagnosis to RRT initiation was a factor that defined the grouping of "early" versus "late", and the problems you pointed out are also our concerns when designing this study. However, in actual clinical work, many patients have developed AKI when they are admitted to ICU, and ICU physicians cannot accurately know when a patient meets the diagnostic criteria for AKI. Therefore, the "early" or "late" initiation of RRT depends on the time when the patient actually develops AKI (which is very difficult to accurately obtain). For example, a patient with stage 3 AKI is transferred from home to the intensive care unit of the hospital and needs to initiate RRT immediately, the time from the diagnosis of AKI to the initiation of RRT may be short, but it does not mean that the patient is not serious. We believe that the severity of the disease is what really determines the "early" or "late" initiation of RRT. This was also one of the rationales for designing the study groups.

b. Indeed, in previous studies on the timing of RRT initiation, the Criteria of the "delayed" group included patients with emergent indications for dialysis. A review summarized these, see Table2, line - Criteria for late KST, Bouchard J, Mehta RL. Timing of Kidney Support Therapy in Acute Kidney Injury: What Are We Waiting For? Am J Kidney Dis 2022; 79:417-26. and our

grouping criteria were also based on these studies, a total of 27 of our included subjects had urgent indications for RRT.

c. We acknowledge that there was no statistically significant difference in fluid overload between the two groups. Similar to question "a", RRT was initiated within 24 hours after ICU admission in some patients. Because of the short time, the total fluid balance would also not be high, but it does not indicate that these patients are less critical. At the same time, due to the current treatment concept of restrictive volume management, we believe that this parameter of %FO is not suitable for current clinical management. We discussed this in the manuscript: "In our current study, some patients had clinical signs and symptoms suggestive of FO. However, because these patients received RRT within 24 hours after ICU admission and had restrictive fluid management, the median %FO was 1.36% in the early RRT group and 0.76% in the delayed RRT group, far less than 10%. Thus, we believe that the threshold of %FO >10% is not suitable for assessing whether there is FO in adults. The recent STARRT-AKI study (9) and AKIKI2 study (10) revealed a mean cumulative fluid balance between 1.5 and 3 L. It also illustrates that fluid overload is not a common phenomenon in patients with AKI today. Therefore, FOP was adopted in place of %FO to assess whether patients had FO (18)." (Page 11, line 327-336.).
In addition, I am very sorry that we may mislead the reader due to the unclear description, that is, FO is a clinical state, and the two indicators reflecting FO are %FO and FOP. We have added a note in the discussion of the manuscript (Two parameters can be used to assess fluid overload in patients: %FO and FOP, Page 10, Line 320.), hoping that we can explain it.

d. Based on our clinical finding that %FO is not suitable for the evaluation of fluid overload, we incorporated the concept of fluid overload present (FOP) into the criteria for the classification of "early" and "delayed", which has also been proposed in previous studies. Vaara ST, Ostermann M, Bitker L, et al. Restrictive fluid management versus usual care in acute kidney injury (REVERSE-AKI): a pilot randomized controlled feasibility trial. Intensive Care Med 2021; 47:665-73. We believe that FOP is more suitable for evaluating the severity of patients. Finally, FOP combined with AKI stage was adopted as the grouping criterion.
We discussed this in the manuscript: "Patients with stage 3 AKI and fluid overload present (FOP) and/or meeting the emergency indications for RRT were assigned to the delayed RRT group, patients with stage 1 AKI or stage 2 AKI and without urgent indications for RRT and patients with stage 3 AKI without FOP and without urgent indications for RRT were enrolled in the Early RRT group. FOP is defined as the presence of pitting edema and/or positive fluid equilibrium with oxygenation index which is defined as Arterial partial pressure of oxygen divided by the fraction of inspired oxygen [PaO2/FiO2 (P/F)] <200 mmHg (18)." (Page 5, line 144-151) and "In our current study, some patients had clinical signs and symptoms suggestive of FO. However, because these patients received RRT within 24 hours after ICU admission and had restrictive fluid management, the median %FO was 1.36% in the early RRT group and 0.76% in the delayed RRT group, far less than 10%. Thus, we believe that the threshold of %FO >10% is not suitable for assessing whether there is FO in adults. The recent STARRT-AKI study (9) and AKIKI2 study (10) revealed a mean cumulative fluid balance between 1.5 and 3 L. It also illustrates that fluid overload is not a common phenomenon in patients with AKI today. Therefore, FOP was adopted in place of %FO to assess whether patients had FO (18)." (Page 11, line 327-336.).
In addition, our conclusion is consistent with the previous large RCT that classified "early" or "delayed" RRT based on AKI stage, and early initiation of RRT did not improve prognosis.
Your views have given us great inspiration, and we hope that our explanation can gain your approval.
Changes in the text: We add "Two parameters can be used to assess fluid overload in patients: %FO and FOP," in the discussion section of the manuscript, please see Page 10, line 320.

2. The study seems to be significantly underpowered.

a. The authors conducted power calculations by picking the lowest possible value from the "early" group, which was from ELAIN, and comparing it to the highest possible value for the delayed with dialysis groups, which came from IDEAL. To hypothesize a 30% absolute difference in mortality was quite unrealistic, and resulted in a population that was too small for the clinical question. I was able to reproduce the authors' sample size calculations giving 108 patients. Using a more reasonable hypothesis of 10-15% absolute reduction, 400-900 cases would be required. While post-hoc power calculations can be problematic, just to illustrate the point, they suggest this study had only 20% power.

b. Likely as a result, large effect sizes favoring "early" of OR 0.69 unadjusted and 0.73 adjusted are not significant.

Reply 2: Thank you for your advice. Regarding the sample size, we have the following ideas: a. Mortality is the end point of the study, and some continuous variables are also concerned by us. For example, in this study, we also analyzed continuous variables such as the duration of ICU non-mechanical ventilation in the two groups, and the sample size is absolutely sufficient for continuous variables. b. Whether early initiation of RRT was an independent risk factor for 90-day mortality was analyzed in a multivariate binary logistic regression. According to the "10 × EPV (events per variable)" principle and the final number of included independent variables, the sample size was adequate. c. Our study retrospectively analyzed the patients with heart failure complicated with AKI in our center in the past 10 years. Due to the single center, the sample size is limited, but we believe that the actual clinical situation should be reflected, and we also supplemented it in the discussion section of the article.

Changes in the text: We have deleted "According to the data in a previous study (12), we assumed that the 90-day mortality rate of the early RRT group and the delayed RRT group would be 39% and 68%, respectively. Based on this, the calculated sample size of each group was 43 cases when the β was 0.2, the power (Power = 1 – β) was 80%, and the significance level was α=0.05 (2-sided). A dropout rate of 20% of the subjects was considered, at least 108 cases were required", （line 188-193）. And we have added the content of paragraph 6 of the discussion section as follows "First, as a single-center retrospective study, the sample size may need to be expanded further". (Page 12, line 371).

3. There are some additional methodological questions

a. It was unclear how the covariates for the multivariable model were chosen. The Methods seem to suggest that they were chosen based on differences between groups with $p < 0.05$, but there are several variables fitting this definition that were not included.

b. Adjusting for both APACHE II and SOFA is likely to run into issues of collinearity.

c. Adjusting for both early dialysis and time from AKI to CRRT initiation underscores the issue outlined above, that "early" wasn't earlier than "delayed".

Reply 3: Thank you for your advice.

a. The selection of these variables was based on P values and clinical judgment (Some parameters with statistical differences were involved in the grouping criteria of "early" and "late" RRT), and the possibility of collinearity in some parameters was excluded. We have

described this in the manuscript: “Although Scr on ICU admission showed statistically significant differences (P value < 0.01), it was a sub-variable in the APACHE II score and SOFA score on the first day of ICU admission(Table2). some other variables were obtained at the time of RRT initiation, such as Scr, BUN, eGFR, P/F, Peripheral pitting edema, PH, K+, Stage of AKI(all P values <0.05),The differences in these variables between the two groups were related to the grouping criteria we set(Table3).Therefore, they were not included in the multivariate binary logistic regression analysis”.(Page9, Line261-268).

b. We performed multivariate binary logistic regression with the APACHE-II score and SOFA score excluded separately, and the results did not affect our main conclusions. Ultimately, we removed the SOFA score because the APACHE-II score contains more subvariables and is more comprehensive. Modifications have been made in the manuscript where appropriate.

c. In fact, as mentioned in the question answered above, the time from the diagnosis of AKI to RRT does not reflect the severity of the disease. There is no statistically significant difference in the initiation "time" between the two groups, which is in line with the clinical reality, and this is the conclusion we have been trying to confirm. Therefore, in the multivariate binary logistic regression analysis, we included the time from AKI diagnosis to RRT initiation as a variable, and we believed that “Interval from AKI diagnosis to RRT initiation” and “Early RRT” could not substitute for each other.

Changes in the text: Please see Table 5.

4. There are other issues of a more minor nature, but I think these major issues will be difficult to overcome.

Reply 4: Thank you for your constructive suggestions which will promote our progress. We have explained the above questions and revised the manuscript in a suitable place. We look forward to being accepted by you and salute you again.

Reviewer B

The paper titled “Comparison of early and delayed strategy for renal replacement therapy initiation for severe acute kidney injury with heart failure: a retrospective comparative cohort study” is interesting. Early initiation of RRT is not recommended to reduce mortality in AKI patients with HF. However, there are several minor issues that if addressed would significantly improve the manuscript.

Is the grouping and definition of delayed RRT group and Early RRT group in this study reasonable? It is recommended to provide explanations and literature support.

Reply 1: We feel great thanks for your professional review work on our article. Our definition of grouping is based on the findings of our clinical work, that is, it is not appropriate to define "early" and "late" based on time alone, because some patients are in critical condition when they are admitted to ICU from outside the hospital and need RRT immediately. Obviously, judging "early" and "late" by time is not in line with the actual situation, which is confirmed in our manuscript, time from AKI diagnosis to RRT was not a risk factor for 90-day mortality. However, most of the previous studies used the time from enrollment to RRT combined with AKI stage to classify "early or late". the 17th Acute Disease Quality Initiative (ADQI)

Consensus states that Acute RRT should be considered when metabolic and fluid demands exceed total kidney capacity (Patient Selection and Timing of Continuous Renal Replacement Therapy, PMID:27561956, Consensus statement 1.1). So we used the definition of fluid overload present (FOP), which reflects the actual situation of fluid retention in clinical practice[Restrictive fuid management versus usual care in acute kidney injury (REVERSE-AKI): a pilot randomized controlled feasibility trial，PMID：33961058, The fifth row from the last in table 1], combined with the stage of AKI to distinguish "early and late". We have explained this in the manuscript：“The requirement of RRT in patients with AKI and HF is due to the imbalance between kidney demand and reserve (32).”.(Page 11, Line338-339). “FOP is defined as the presence of pitting edema and/or positive fluid equilibrium with oxygenation index which is defined as Arterial partial pressure of oxygen divided by the fraction of inspired oxygen，[PaO2/FiO2 (P/F)] <200 mmHg (18). ”. (Page 5, line148-151).

Changes in the text: We add “So we used FOP combined with AKI stage for grouping” in the discussion section of the manuscript. Please see Page 11, line 340.

What happens to a more-delayed initiation strategy compared to a delay strategy? What mandatory indication are required for the initiation of RRT for the more-delayed strategy? It is recommended to add a description of relevant content.

Reply 2: We have added the content you requested in the introduction section of the manuscript.The details are as follows: “more delayed RRT is an independent risk factor for 60-day mortality in stage3 AKI patients with persistent oliguria for more than 72 hours or blood ureanitrogen concentration (BUN) higher than 112 mg/dL. and the more delayed RRT was defined as the initiation of RRT was postponed until mandatory indication (noticeable hyperkalaemia or metabolic acidosis or pulmonary oedema) or until BUN concentration reached 140 mg/dL.”.

Changes in the text: we have modified our text as advised. (Please see page3, line 87-88 and page 4, line 89-92).

Has this study considered the impact of other factors on RRT time, such as BMI? What are the associations of BMI categories with mortality and starting RRT? If considered in multiple ways, it should make the entire study more complete.

Reply 3: Yes, we considered other factors, such as clinical prediction models, furosemide stress tests, and biomarkers, that have proven to be useful for future RRT initiation strategies. However, due to the sample size, the clinical prediction model cannot be established in this study, and furosemide stress test and biomarkers need to be prospectively studied. So, we chose the grouping method used in this study.

You have provided us with very professional and valuable suggestions, and we have consulted relevant materials, BMI can affect the clinical outcome of AKI patientsthe hospital prognosis of AKI and AKI-RRT patients after cardiac surgery was best when their BMI was in the 24-28 range (Role of Body Mass Index in Acute Kidney Injury Patients after Cardiac Surgery, PMID: 29344022.). Another study of COVID-19 complicated with AKI suggested that patients undergoing RRT had higher BMI. (AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19, PMID: 33067383).

We have added relevant content on BMI in the discussion section of the manuscript as suggested by you. Thank you again for your valuable advice.
Changes in the text: we have modified our text as advised. (Please see page 11, line 344-351).

What are the roles of acute kidney injury biomarkers to guide RRT initiation? It is recommended to add relevant content to the discussion.
Reply 4: Thanks for your guidance, we have added relevant content: Biomarkers have a role in determining when to initiate RRT in critically ill patients with AKI. Although some biomarkers have shown predictive ability for RRT in critically ill patients with AKI, the evidence is not strong enough to prove that they can be used routinely in clinical practice to guide the decision of when to initiate RRT (37). The RUBY study(38) found that urinary C-C motif chemokine ligand 14 (CCL14) had a strong ability to predict stage3 AKI lasting 72 hours or more, The area under the receiver operating characteristic (ROC) curve of CCL14 was 0.83, and higher concentration of CCL14 was associated with an increased risk of a composite endpoint consisting of adverse events such as RRT initiation or death within 90 days, the CCL14 is expected to be used in clinical decision making in the future.
Changes in the text: we have modified our text as advised. (Please see page 11, line 350-355 and page 12, line356-359).

This study is a single-center retrospective study. It is recommended to conduct a multi-center, large sample, prospective study and external verification.
Reply 5: Thanks for your suggestion, we have added the corresponding content in the discussion section of the manuscript: “A multi-center, large sample, prospective study and external verification is needed.”
Changes in the text: we have modified our text as advised. (Please see page 12, line371-372).

The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “A narrative review of care for patients on maintenance kidney replacement therapy during the COVID-19 era, PMID: 34417996”. It is recommended to quote the articles.
Reply 6: Thank you for the references you provided to make our study more convincing. We have cited them, and the numbers of other references have been corrected.
Changes in the text: we have modified our text as advised. (Please see page 3, line 73 and page 13, line420-422).

In the introduction of the manuscript, it is necessary to clearly indicate the knowledge gaps and limitations of prior study and the clinical significance of this study.
Reply 7: Thanks for your suggestion, we add “the main objective was to provide evidence for clinical optimization of the timing of RRT initiation in AKI patients with HF.”
in the last paragraph of the introduction. In the manuscript (page 4, line 102-104), we've already mentioned: Subgroup analysis of previous studies (7-11) did not investigate whether patients with heart failure complicated with AKI could benefit from early RRT.
We hope these revisions will gain your approval.
Changes in the text: we have modified our text as advised. (Please see page 4, line107-108).

Reviewer C

1. Abstract

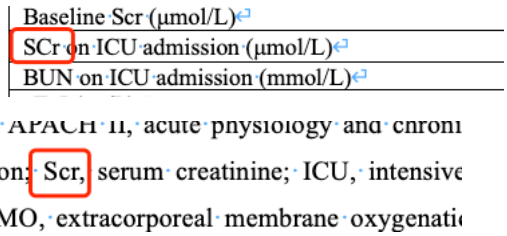
Please defined OR and CI in the abstract.

Reply: Thank you for your hard work and We apologize for our negligence， We have defined it and modified it in the text.

Changes in the text: Please see page 2, line 56-57.

2. Table 2

Please unify the word.



Reply: Thank you for the reminder, we have modified it in the text, the same problems in the manuscript are also solved.

Changes in the text: Please see page 5, line 135; page 9, line 261; Page 17, the seventh-to-last row of Table 2.

3. Table 5

Please explain ICU in the table footnote.

Reply: We are very sorry for the trouble caused by our imperfect work. The explanation has been added in the text.

Changes in the text: Please see page 19, footnote of Table 5.