Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-2352

Reviewer A:

Comment 1:

This is a small study this must be very strongly stated in text to avoid over stating findings. This is also a non randomizes Observational study the potential for bias is large as such. This is a worthy target of investigation and valuable for liver transplant literature. However the study that settles this question likely will be an order of magnitude larger as far as the n

Reply 1:

We are truly grateful to yours critical comments and thoughtful suggestions. Although you didn't finish your last sentence, we probably know what you want to say. Yeah, this is a small and non randomizes observational study. So we've stated that in the discussion section: "This paper had several limitations. This was a retrospective, single-center study with a small number of patients and the short period of time. Thus, there is clearly a requirement for a prospective large scale trial to further understand CRRT for LT-associated AKI in the future.". So we explored the optimum time of initiation of CRRT for AKI after liver transplantation firstly. Limited by the condition of liver transplantation and its complications AKI, it is difficult to carry out a large-scale multicenter randomized controlled study. We hope that this retrospective study provides data that can be used to put forth a tenable hypothesis for optimum time of initiation of CRRT for AKI after liver transplantation. This will serve as a hypothesis generating study providing preliminary data which can be further validated.

Changes in the text:

No

Comment 2:

You should compare clinical differences between early and late crrt initiation groups as statistically significant differences should be readily mentioned

Can add this to table 2 or make a separate table

Reply 2:

Thanks for your thoughtful suggestions. We have compared clinical differences between early and late CRRT initiation groups in Table 2. We have deleted Table 1, changed the previous Table 2 to Table 1.

Changes in the text:

We have deleted Table 1, changed the previous Table 2 to Table 1. We have compared

clinical differences between early and late CRRT initiation groups in Table 2. The corresponding interpretation of Table 2 is also added in the results section and marked in red：“The clinical differences were compared between early and late group（Table 2）”.

Comment 3:

English language revision would be helpful

Reply 3:

We have consulted native English speakers for paper revision before the submission this time in the hope of meeting the language requirements for Journal publication.

Changes in the text:

The language of the text has been polished by native English speakers.

Reviewer B:

Comment 1:

Authors investigated the optimal time of initiation of CRRT after liver transplantation. Authors might have misknowledge of the definition and basic therapeutic principles of the acute kidney injury (AKI) and the renal replacement therapy. Thus, the research is meaningless.

Reply 1:

We are truly grateful to yours critical comments. We defined and graded AKI according to KDIGO criteria, not only by serum creatinine, but also by urine output. As for the basic therapeutic principles of the acute kidney injury (AKI), careful assessment of volume status and hemodynamics are undertaken and treated with intravenous fluids, diuretics, or other means of hemodynamic support as indicated. Some patients with severe AKI will require CRRT. The optimal timing of CRRT is an area of active investigation. Not all AKI patients receive CRRT. In our study, 23 out of 48 AKI patients received CRRT. The optimal timing of CRRT for AKI continues to be debatable.

Especially, there is no report about the optimal initiation timing of CRRT for AKI after liver transplantation. So we explored the optimum time of initiation of CRRT for AKI after liver transplantation firstly. We hope that this retrospective study provides data that can be used to put forth a tenable hypothesis for optimum time of initiation of CRRT for AKI after liver transplantation. This will serve as a hypothesis generating study providing preliminary data which can be further validated. So we think that our research is meaningful.

Changes in the text:

We have changed" AKI was defined according to KDIGO criteria as an increase of serum creatinine by ≥26 μmol/L within 48 h as well as an increase to ≥1.5 times baseline within 7 days." to "AKI was defined according to KDIGO criteria by serum creatinine and urine output" in the method section.

Comment 2:

The definition of AKI is wrong. The urine output is also an important index for the diagnosis of AKI.

Reply 2:

Thanks for yours critical comments. Yeah, The urine output is also an important index for the diagnosis of AKI. We defined and graded AKI according to KDIGO criteria, not only by serum creatinine, but also by urine output. We have changed" AKI was defined according to KDIGO criteria as an increase of serum creatinine by ≥26 μmol/L within 48 h as well as an increase to ≥1.5 times baseline within 7 days." to "AKI was defined according to KDIGO criteria by serum creatinine and urine output" in the method section.

Changes in the text:

We have changed" AKI was defined according to KDIGO criteria as an increase of serum creatinine by ≥26 μmol/L within 48 h as well as an increase to ≥1.5 times baseline within 7 days." to "AKI was defined according to KDIGO criteria by serum creatinine and urine output" in the method section.

Comment 3:

The reference for KDIGO guideline is wrong. Please correct it.

Reply 3:

Thanks for pointing out this mistake. We have corrected it.

Changes in the text:

We have changed reference 8 to "8.Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. Section 2: AKI definition. Kidney Int Suppl. 2012;2:19–36.".

Comment 4:

The standard of grouping is wrong. The urine output might be affected by various factors, such as the original kidney diseases, diuretics, infections and so on. Thus, it is unreasonable to judge the optimal time of initiation of CRRT according to the urine output.

Reply 4:

The optimal timing of CRRT for AKI continues to be debatable. And the standard of

grouping is debatable. Timing of CRRT based on time (time from ICU or hospital admission to CRRT) and urine output were explored in several studies, in order to identify which parameter could be more useful to initiate CRRT. Timing of CRRT based on urine output seems a more physiological approach and recent studies have emphasized the importance of urine output as a clinical AKI biomarker. Starting CRRT before low urine output setting could hypothetically prevent volume overload which is a well-known mortality predictor in patients with sepsis with or without AKI. So we define the timing of CRRT based on urine output, which is more reasonable.

Changes in the text:

No

Comment 5:

KDIGO guideline also describes the dialysis indications of AKI. Why authors still investigated the indications of CRRT again?

Reply 5:

Thanks for your query. KDIGO guideline did not describe the dialysis indications of AKI specifically. AKI patients who started CRRT treatment were classified as stage 3 AKI only, and there was no clear indication of the timing of CRRT treatment? what was the index to judge the timing of CRRT treatment? So the optimal timing of CRRT for AKI continues to be debatable. And the standard of grouping is debatable. So we still investigated the indications of CRRT. At the same time, a study of Pérez-Fernández X et al. indicated tha among patients with stage 3 AKI, survival is lower when CRRT is started in the setting of low UO (< 0.05 mL/kg/h), while timing itself (from admission) is not. These results further inform the debate about when to initiate CRRT. So we think that our research is meaningful.

Changes in the text:

No

Comment 6:

How many patients have chronic disease, glomerular nephritis and other kidney diseases before the liver transplantation?

Reply 6:

As for chronic diseases, as shown in Table 1 and 2, 14 patients had diabetes, 7 had hypertension, and there was no significant difference between AKI and Non-AKI group. There was no significant difference between the early and late CRRT group. Because of concerns about the impact on outcomes, we did not include patients with chronic kidney disease in our study. Therefore, the influence of glomerular nephritis and other kidney diseases on the result is excluded.

Changes in the text:

No

Comment 7:

What is the causes of AKI of each patient? Prerenal AKI, acute tubular necrosis, acute glomerular nephritis, acute tubulointerstitial nephritis, postrenal AKI or others? The different type of AKI might affect the urine output.

Reply 7:

Several risk factors for post-LT AKI have been identified in varying populations. It is unlikely that post-LT AKI is caused by a single insult, but rather is of multifactorial origin with recipient, graft, perioperative, and postoperative factors contributing to its development. Patients with end-stage liver disease have an increased risk of developing AKI. It has been hypothesized that hepatic ischaemia reperfusion injury (HIRI) is one of the driving forces of post-LT AKI. Liver transplantation is high-risk surgery with a significant risk of hypotension, tissue hypoperfusion and blood loss, which are known risk factors for postoperative AKI. Calcineurin inhibitors (CNIs) are the mainstay of immunosuppression regimens after liver transplantation. However they are known for their acute and chronic nephrotoxicity. In patients with AKI, kidney biopsy remains an option to better determine the type and extent of lesions and to identify underlying kidney changes; however, kidney biopsy is difficult to perform in the population of liver transplantation because of coagulation abnormalities. Urine output is an important index to judge AKI degree and whether CRRT is performed.

Changes in the text:

No

Comment 8:

Authors grouped patients according to the criteria of urine output of 0.05ml/kg/h. Why? Please provide the reference or reasons in detail. Should it be 0.5ml/kg/h ?

Reply 8:

We grouped patients according to the study of Pérez-Fernández X(Pérez-Fernández X, Sabater-Riera J, Sileanu FE, et al. Clinical variables associated with poor outcome from sepsis-associated acute kidney injury and the relationship with timing of initiation of renal replacement therapy. J Crit Care. 2017;40:154-160.). In this study, initiation based on days from ICU to CRRT was compared to initiation based on UO in the 24 h prior to CRRT initiation. Initiation based on days from ICU to CRRT showed no differences between the “early” group (0 to 2 days) and the “late” group (3 to 5 days) ($p = 0.765$), whereas initiation based on UO showed important differences in 90-day survival between patients, in whom CRRT was started with UO $\leq$ 0.05 mL/kg/h, and in patients in whom CRRT was started with UO > 0.05 mL/kg/h ($p = 0.019$). So we grouped patients according to the criteria of urine output of 0.05ml/kg/h.

Changes in the text:

No

Comment 9:

Please state inclusion and exclusion criteria of patients clearly in the Methods.

Reply 9:

Thanks for your suggestion. Patients who underwent liver transplantation between January 2018 to March 2019 at The First Affiliated Hospital, Sun Yat-Sen University (Guangzhou, China) were included. Patients with chronic kidney disease or receiving preoperative CRRT or kidney transplantation before were excluded. Eventually 173 patients were included in this study.

Changes in the text:

We change “The records of 173 patients who received LT at The First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China) from January 2018 to March 2019 were retrospectively reviewed.” to “Patients who underwent liver transplantation between January 2018 to March 2019 at The First Affiliated Hospital, Sun Yat-Sen University (Guangzhou, China) were included. Patients with chronic kidney disease or receiving preoperative CRRT or kidney transplantation before were excluded. Eventually 173 patients were included in this study.” in the Methods.

Comment 10:

Please delete Table 1.

Reply 10:

Thanks for your suggestion. We have deleted Table 1.

Changes in the text:

We have deleted Table 1, changed the previous Table 2 to Table 1.

Comment 11:

P values should not be 0.000. Authors should correct all $P = 0.000$ to $P < 0.001$.

Reply 11:

Thanks for your suggestion. We have corrected all $P = 0.000$ to $P < 0.001$.

Changes in the text:

We have corrected all $P = 0.000$ to $P < 0.001$.

Comment 12:

Abbreviations should be shown in full length at the first appearance. Please provide full titles of KDIGO, RIFLE, AKIN and MELD.

Reply 12:

Thanks for your suggestion. We have provided full titles of KDIGO, RIFLE, AKIN and MELD: the Risk, Injury, Failure, Loss and End-stage (RIFLE) definitions, the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Model for end-stage liver disease(MELD)

Changes in the text:

We add full length of abbreviations(KDIGO, RIFLE, AKIN and MELD) at the first appearance.

Comment 13:

The English writing should be further improved.

Reply 13:

We have consulted native English speakers for paper revision before the submission this time in the hope of meeting the language requirements for Journal publication.

Changes in the text:

The language of the text has been polished by native English speakers.