Reviewer's report

Title: Delay in renal replacement therapy initiation increases mortality in patients developing acute kidney injury after liver transplantation

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Reviewer: Steven Weisbord

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Narciso and colleagues report on the association of timing of RRT institution for AKI and mortality. The issue of timing of RRT and its effect on outcomes in AKI is highly clinically relevant. I have the following comments on this manuscript:

1) As is the case with past observational studies on this topic, this study does not seem to be able to address the salient issue of whether the association of earlier RRT initiation with improved outcomes is related to the fact that some of the patients started on dialysis earlier would have recovered kidney function and not required dialysis at all. Inclusion of such patients in the "early" initiation group may result in improved outcomes. I do not believe that observational studies such as this one are able to account for this significant confounding issue. The relevance of this issue to the findings in this study warrant much greater emphasis and discussion.

2) It is not clear to me why the investigators defined the time variable as time to RRT or peak creatinine. It appears that time to peak creatinine is a surrogate for (although may not definitively represent) duration of AKI. Past studies (Coca et al. etc) have demonstrated that duration of AKI is associated with adverse outcomes. Drawing conclusions on the timing of RRT from analyses of time to peak creatinine seems somewhat unjustified. This approach needs to be better explained. Moreover, the authors should better describe how the analyses of time to peak creatinine related to their findings on the time to RRT initiation.

3) The authors cite the use of AKIN criteria for their definition of AKI. However, AKIN has a series of sequential categories based on severity of kidney dysfunction. It is not made clear in the manuscript which exact category of AKI was used to warrant the initiation of RRT. Were patients who met AKIN stage 1 or 2 started on RRT? If so, how did the investigators determine that the patient was not going to recover kidney function without requiring RRT? Furthermore, was AKIN stage 1 used to determine the time from diagnosis of AKI to need for RRT or peak creatinine? This needs to be made much clearer.

4) It appears that the majority of patients in this study who developed AKI reached stage 1 of the AKIN definition as described in the results (48% reached stage 1). Were these patients started on RRT without more progressive AKI? If so, what were the reasons they were started on RRT? Furthermore, based on table 2, it appears that there were more patients in the <7 days group who required RRT than who reached stage 3 AKI. The authors should explain this in greater detail.
5) How was "renal dysfunction prior to LTx" (as described in the second paragraph of the Results section) distinguished from AKI prior to LTx? Furthermore, what was the cause of renal dysfunction prior to LTx in the patients who were included in the analysis? There are prior data that patients with AKI and background CKD have better outcomes than patients with AKI that develops in the setting of intact baseline kidney function. Were there differences in this variable based on the timing of RRT initiation?

6) The significance of the generation of ROC analysis is unclear. Specifically, the sensitivity and specificity reported (44% and 77%) and the area under the ROC (0.6) are relatively poor. Use of the 7 day cut-off seems quite problematic given these very marginal estimates.

7) Given the significant limitations in these data and the important potential confounding factors (see point #1) above, the conclusions that the authors draw that delaying RRT initiation increases mortality is too strong. I would suggest substantially modifying the conclusions to reflect the important limitations of observational data for addressing this clinical question. Furthermore, the authors state that patients with stage 2 or 3 AKI whose recovery of kidney function is unlikely in 4 days, should be started on RRT. However, prediction of whether and when kidney function will recover can be difficult in clinical practice. I would suggest modifying this section to better reflect the findings of this study within the limitations of the data.

8) How was long-term mortality assessed? Was there any risk for loss to follow up that would have impacted the assessment of 1 year mortality?

9) In the second to last paragraph of the discussion, the authors propose a very specific period of time (3 days, 17 hours, 22 minutes) that the risk of mortality doubles. The precision of this estimate seems somewhat questionable from the other data presented. Moreover, given the inherent limitations in observational data, it seems very unlikely that an estimate such as this would be generalizable or able to be validated. I would suggest modifying this statement to better reflect the difficulty in predicting a time frame for risk of death with AKI based on observational data.

10) The secondary focus of the manuscript on other factors associated with mortality seems of lesser interest. I would suggest deleting some of this from the manuscript.

11) There seems to be a fair amount of "process/background" data presented in the first few paragraphs of the Results section. Much of this could be contained in a table.

12) The authors present their analyses as "multivariate" – are these "multivariate" or "multivariable" analyses?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

none