Author's response to reviews

Title: The incidence and risk factors of acute kidney injury after hepatobiliary surgery: a prospective observational study

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Author's response to reviews: see over
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Title: The incidence and risk factors of acute kidney injury after hepatobiliary surgery: a prospective observational study

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The authors conducted an observational prospective cohort study to evaluate the incidence of clinical and subclinical AKI after hepatobiliary surgery, to determine the risk factors for AKI, and study the significance of subclinical AKI. In general, the manuscript is well written, the methodology and aims are clear, and the scientific design and statistical methods are appropriate. In terms of content, the authors evaluated a novel concept of the significance of subclinical AKI using urinary biomarkers. The following points are offered for the authors’ consideration:

1. The authors excluded patients with chronic kidney disease with eGFR of < 60ml/min/1.73m². The reason for this is not clear in the manuscript and may result in underestimation of the actual incidence of AKI following hepatobiliary surgery. The definition of AKI is based on changes in eGFR and urine output regardless of the baseline kidney function. Please clarify the rationale behind excluding these patients, and mention in the discussion as a limitation.

We did not include patients with eGFR of <60/ml/min/1.73m2 because patients with CKD are reported to be prone to develop AKI and AKI is a risk factor of the CKD progression. We thought that including patients with decreased eGFR can be a confounding factor in interpreting the incidence of post-operative AKI and the 6 months renal outcome post surgery. We already mentioned that we only included patients with normal renal function as a limitation, but as you commented, we added more explanation in the discussion section (page 14, line 320-322).

2. Regarding the definition of subclinical AKI in the methodology section, although this definition has been used before, the authors need to include a reference and discuss the validity of the definition to indicate that their definition has been used in other published literature.

We inserted a reference that showed that patients with subclinical AKI had increased risk of
death or need for dialysis in ICU setting (reference number 2, page 5, line 105-107). We also discussed about our data showing even subclinical AKI following hepatobiliary surgery resulted in significantly longer hospital stay and worse 6 months eGFR compared to patients without AKI (page 13, line 290-294).

3. Ten of 131 (7.6%) of the cohort had AKI following the surgery where 5 of them had AKIN stage 1. On the other hand 20/131 (15.3%) of the cohort had a liver transplant. The authors did not specify how many transplant patients had AKI. The incidence of AKI following liver transplant can range from 17-96%. I am concerned that most AKI occurred in this group of patients which makes the generalization of the authors’ results on the population of hepatobiliary patients invalid.

As you mentioned, clinical AKI mostly occurred in patients who underwent liver transplantation (8 out of 10). First, we also considered excluding transplant patients but as we focused on patients with subclinical AKI and decided to make AKI group including patients with both clinical and subclinical AKI, we did not exclude transplant patients. Instead, we reported the composition of diseases and types of operation of our study population in Table 2 and Table 3; Table 3 shows that 16 of 20 transplant patients were grouped in AKI group. Also, we adjusted liver transplantation when analyzing predictive or risk factors. And most patients with subclinical AKI underwent non-transplant surgery.

We already mentioned about this in our limitations section. According to your comment, we added the incidence clearly in the result section (page 7, line 146).

<table>
<thead>
<tr>
<th></th>
<th>Clinical AKI (n=10)</th>
<th>Subclinical AKI (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation</td>
<td>8/20 (40.0%)</td>
<td>8/20 (40.0%)</td>
</tr>
<tr>
<td>Other surgeries</td>
<td>2/111 (1.8%)</td>
<td>34/111 (30.6%)</td>
</tr>
</tbody>
</table>

4. The authors chose to obtain both serum and urinary NGAL where serum NGAL did not show any significant predictive value. Both urinary and serum NGAL perform almost equally in predicting AKI. Can the authors comment on this discrepancy in their results and the potential roles of serum versus urine NGAL in predicting AKI in their population?

As far as we know of, performance of urine NGAL in predicting AKI has been shown to be superior than plasma NGAL. Our previous study in ICU patients[5] and another study with liver transplant patients[6], urine NGAL was more useful than plasma NGAL in predicting AKI or prognosis. Under physiologic condition, NGAL is expressed in low concentration in kidney,
liver, lung and gastrointestinal tract[1]. Since plasma NGAL can be increased due to release from other diseased organs such as liver, we think specificity of urine NGAL might be better than that of plasma NGAL in terms of detecting or predicting kidney injury in patients who had underlying liver disease. We added our comment on this in the discussion section (page 10, line 228-233).

5. It is not clear how the authors elected to include the variables in the multivariate regression model. Many of the chosen variables were insignificant in univariate analysis though it was included in the multivariate analysis.

It is well known that episode of AKI is the most important factor in the development or progression of CKD. We aimed to determine the predictors of 6 months renal outcome in our study population regardless of the occurrence of postoperative AKI. This is the reason why we included many variables that are not significant in univariate analysis. However, inter-related factors were excluded. For example, only MELD-Na score was included as representative variable for liver status while all other laboratory values were not included. And Liver transplantation was needed to be adjusted as you mentioned in your 3rd comment.
The concept of evaluating subclinical AKI is somewhat innovative and potentially clinically relevant. Although at these sample sizes, conclusions and validation of results is difficult.

1. I would ask authors however to describe the differences in characteristics - baseline and operative - between clinical and subclinical AKI. They have reported the outcomes in this way - and it is interesting that the LOS is higher in subclinical AKI compared to no AKI.

We attached the comparison table as a supplementary data and mentioned the differences between clinical and subclinical AKI groups in our manuscript (result section; page 8, line 176-180).

2. Do the authors have information on serum NGAL? Does the hepato-biliary tract release NGAL?

We presented the level of serum NGAL prior to operation and 24hr after the operation in Table 1. It showed no significant differences between AKI and non-AKI groups. Yes, under physiologic condition, NGAL is expressed in low concentration in kidney, liver, lung and gastrointestinal tract and there is possibility that hepatobiliary tract can release NGAL, though it has not been tested[1]. Future studies are needed to clarify this.

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

Quality of written English: Acceptable

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

Declaration of competing interests: no competing interests.

References


