Author’s response to reviews

Title: Impact of thyroid function on Cystatin C in detecting acute kidney injury: a prospective, observational study

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Author’s response to reviews:

Dear Professors,

I am very grateful for your assessments on the manuscript. According to your advice, we amended the relevant parts in manuscript, with the changed text highlight in revised manuscript. A copy of revised manuscript without the changed text highlighted was also appended. All your comments were answered below.
For comments from Ziad M. El-Zoghby (Reviewer 1):

1. In the text and Figure 1, It would be less confusing for the readers to label the "established AKI" as "AKI prior to ICU admission" and those with "late onset AKI" as "AKI post ICU admission."


2. Table 1 reports the median and IQR of the thyroid hormone levels. Can you specify the proportion of patient who had abnormal thyroid hormone levels? Was it different between AKI and non-AKI groups?

   Response: Thank you for your comment. In the study, low T3 syndrome occurred in 61.2% of the AKI patients (n=246), and 43.1% of the non-AKI patients (n=404). According to the chi-square test, it was significantly different between AKI and non-AKI group. (Table 1, Result section, line 219, page 12)

3. On multivariate linear regression analysis, sex is negatively associated with cystatin C. What was the reference group? Please specify if male or female.

   Response: Thank you for your comment. On both bivariate and multivariate regression analysis, sex is negatively associated with cystatin C, the reference group is male. This would be labeled in the revised manuscript. (Table 2, Table 3)

4. Since FT3 and TT3 are closely correlated which each other, they probably should not be included both in the multivariate model to avoid misfitting the model.
Response: Thank you for your criticism. The multivariate linear regression analysis was used in the prior study (Wang F. et al. The impacts of thyroid function on the diagnostic accuracy of cystatin C to detect acute kidney injury in ICU patients: a prospective, observational study. Crit Care. 2014;18(1): R9), which FT3, TT3 were also included in the analysis. For further confirm the result, we used the same statistical analysis.

5. Can you explain why TT3 was negatively correlated with cystatin C in the bivariate analysis but positively correlated with it in the multivariate analysis? This is confusing and lead to some doubt regarding the robustness of the results / statistical analysis.

Response: Thank you for your criticism. The reason why TT3 was positively correlated with cystatin C in the multivariate linear regression analysis was that collinearity existed in the analysis, which might cause the misfitting problem that was proposed in the question 4. Although we used the stepwise analysis to reduce the misfitting problem, the collinearity still existed. The multivariate analysis in this study can only explain that FT3 and TT3 are statistically associated with cystatin C, but the detailed correlation between them should be further explored. Nevertheless, we believe that the study presents considerable value in clinical practice.

For comments from Moritz Schanz (Reviewer 2):

1. eGFR-Formula: Why did you use the MDRD-Formula for eGFR calculation? CKD-EPI seems to be more reliably in reflecting the real GFR in eGFR around 60 ml/min. (PMID: 22560843).

Response: Thank you for your question and suggestion. Since eGFR was calculated by the MDRD-Formula in our prior research studies, it was calculated with the same way in this study. However, because the CKD-EPI creatinine equation is more accurate than the MDRD formula, we have recalculated eGFR with CKD-EPI, and the result would be corrected in the revised manuscript. (Table I, Method section, line 150, page 8 and Reference section, line 490, page 24)

2. It would interesting if you could report in how many patients AKI diagnosis was based on serum creatinine, on urine output or both. Would it affect your results

Response: Thank you for your reminding. Since the urine output criteria had limited sensitivity when diuretics were administrated, the AKI diagnosis were based on serum creatinine in this study. Therefore, the result would not be affected. This would be illustrated in the revised manuscript. (Method section, line 164, page 9 and Reference section, line 498, page 24)

3. Minor point: Page 17 line 313: Looking at your reference list, it seems that you mean Schanz et al. instead of Moritz et al.

Response: I am so sorry about the mistake, and thank you for your pointing out. The mistake has been corrected in the revised manuscript. (Discussion section, line 314, page 17)

Additionally, we modified an error of legend of Table 6 "859 patients with low T3 syndrome, with FT3<3.80 pmol/L, FT4 and TSH within or lower than the normal range, and 703 patients without low T3" into its correct form of "650 patients with low T3 syndrome, with FT3<3.80 pmol/L, FT4 and TSH within or lower than the normal range, and 689 patients without low T3" in revised manuscript (Table 6).

We sincerely appreciate your insightful and constructive comments and suggestions. We believe that these have greatly strengthened the paper. Thank you again for taking time to review this paper.

Sincerely,

Chunbo Chen