

**Title:** Acute kidney injury in traumatic brain injury intensive care unit patients

**Journal:** World Journal of Clinical Cases

## **Response to Reviewers' comments**

Dear Editor,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,

## Reviewer #1

**Comment 1:** *Comments Page 3 line 11: Replace the word (prognosis) with (the in hospital mortality rate) in the sentence (with prognosis of patients with TBI). As you investigated the in hospital mortality rate as an indicator for prognosis. So please unify.* **Response:** We thank the Reviewer for the comment. It was revised as suggested.

**Comment 2:** *Page 3: Methods need to be rewritten as you wrote the results instead of methods. So this paragraph (From 1648 patients, 291 (17.7%) had AKI, According to KDIGO. The highest incidence of AKI was found by KDIGO (17.7%), followed by AKIN (17.1%), RIFLE (12.7%), and CK (11.5%) (P=0.97). Concordance between KDIGO and RIFLE/AKIN/CK was 99.3%/99.1%/99.3% for stage 0, 36.0%/91.5%/44.5% for stage 1, 35.9%/90.6%/11.3% for stage 2, and 47.4%/89.5%/36.8% for stage 3.) should be added to the paragraph of results. This is a suggestion to write the methods: This was a retrospective study of patients admitted to the ICU for neurotrauma from 2001 to 2012. 1648 patients were included.*

**Response:** We thank the Reviewer. The Abstract was revised accordingly.

**Comment 3:** *Based on baseline SCr, the subjects in this study were assessed for the presence and stage of AKI using RIFLE [12], AKIN [13], CK [14], and KDIGO [18]. Page 3 lines 28 and 29: Please be more focused on your conclusion so rephrase it. For example (this study revealed that KDIGO is the best method to define AKI in patients with TBI). Page 6, line 3: The word explored in the sentence (among TBI patients' needs further explored) should be changed to (exploration). Page 7, line 10: Remove the sentence; (The outcome of this study was in-hospital mortality). Page 11, line 3: Replace The word sensitive in the sentence (the highest incidence of AKI and was more sensitive than RIFLE, CK,...). To be (the highest incidence of AKI and was able to detect more patients than RIFLE, CK,...). Because the words sensitive or specific have different statistical bases.*

**Response:** We thank the Reviewer for the comment. The corrections were made as suggested by the Reviewer.

## Reviewer #2

***Comment 1:** Did the authors evaluate urine output as AKI criteria? - I wonder that although performed in China, the percentage of Asian patients enrolled in this study is so limited. Any comments?*

**Response:** We thank the Reviewer for the comment. UO was not used as the criterion for AKI in this study because UO changes are too much affected by other factors to be accurate. Indeed, patients with TBI in the ICU are often under strict fluid management. In addition, they often receive mannitol to reduce intracranial pressure, but mannitol has an impact on the UO. Therefore, the UO loses its meaning in such patients.

***Comment 2:** I think that, at least theoretically, traumatic brain injury (TBI) encompasses different clinical conditions. Is it not possible that these different conditions can impact AKI development and patients' outcomes?*

**Response:** We thank the Reviewer. It is true that TBI encompasses different conditions and severity. Unfortunately, because of the retrospective nature of the study, many details were unavailable for the proper classification of the cases. ICD-10 classification has limitations and is dependent upon proper coding by the staff. Future studies will have to answer this point.

***Comment 3:** In the multivariate analysis, I think that sCr value and UO should not be considered as covariates being included in the definition of AKI.*

**Response:** We thank the Reviewer. We deleted sCr value and UO as covariates (new Table 7).

***Comment 4:** Figure 1, especially the table, is difficult to understand. Simplify it or explain it in more detail.*

**Response:** We thank the Reviewer for the comment. Each number in the figure represents the number of patients correctly identified with AKI by the different definitions represented by the colored circles. For example, 101 patients are included in all four circles, meaning that they have been correctly classified by all four definitions, while 83 patients were correctly identified by RIFLE, AKIN, and KDIGO. It was clarified in the Figure 2 legend.

***Comment 5:** Please add significance to Figure 4*

**Response:** We thank the Reviewer for the comment. We added the descriptions of staging in Figure 4. Stage 0 is considered no AKI. Stage 1: is at risk. Stage 2 is injury. Stage 3 is failure. There were no statistically significant differences among the four variables.

***Comment 6:** The authors should add units of measurement in the tables - Table 5 is hard to understand and should be explained in more detail (for example, what does it*

*mean R/Stage1?)*

**Response:** We thank the Reviewer. We added the units of measurement in the tables and added the descriptions of staging in Table 5.

*Comment 7: Finally, I think that the authors should discuss more in detail the possible explanations of the lack of association between AKI staging and prognosis*

**Response:** We thank the Reviewer. In the present study, KDIGO did not improve the predictive performance of in-hospital mortality, i.e., the in-hospital mortality increased with the increasing stage in all four definitions. On the other hand, the associations disappeared for all four definitions in the multivariable regression analyses after adjusting for ethnicity, age, sex, Elixhauser score, SAPS II, SOFA, GCS, craniotomy, max creatinine, creatinine at admission, use of antiplatelet drugs, anticoagulant, vancomycin, ARB/ACE-I and aminoglycosides, transfusion, red blood cell, PLASMA, and shock. Therefore, the results mean that one or multiple factors included in the adjusted analyses are a stronger predictor of mortality than AKI in patients with TBI. Besides, clinically, death attributable to AKI is rare in TBI patients, which may explain the lack of association between the four definitions and in-hospital mortality. Osmotic therapy during ICU stay appears to affect the mortality due to AKI <sup>[1]</sup>. A recent study suggested that AKI stage was associated with mortality in patients with TBI, but not AKI duration or AKI burden; in addition, most deaths occurred during the first 3 days of ICU stay <sup>[2]</sup>. The use of renoprotective measures affects the mortality due to AKI in patients with TBI <sup>[3]</sup>. It was clarified in the Discussion, just before the Limitations.

## **Editor**

**Comment 1:** *Comments Page 3 line 11: Replace the word (prognosis) with (the in hospital mortality rate) in the sentence (with prognosis of patients with TBI). As you investigated the in hospital mortality rate as an indicator for prognosis. So please unify.* **Response:** We thank the Editor. The corrections were made as suggested.

**Comment 2:** *The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;*

**Response:** We now provide all figures in a .ppt file.

**Comment 3:** *The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text;*

**Response:** We added the Article Highlights section.

**Comment 4** *It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, the authors must revise the reference list accordingly;*

**Response:** We revised the references. There are now no more than three references from the same journal.

**Comment 5** *Please provide the Institutional Review Board Approval Form in Chinese.*

**Response:** We are now providing the original ethical approval.

## References

1. Robba C, Banzato E, Rebora P et al. Acute Kidney Injury in Traumatic Brain Injury Patients: Results From the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Study. *Crit Care Med* 2021; 49: 112-126. doi: 10.1097/CCM.0000000000004673. PMID: 33060506.
2. Wang R, Zhang J, Xu J et al. Incidence and Burden of Acute Kidney Injury among Traumatic Brain-Injury Patients. *Risk Manag Healthc Policy* 2021; 14: 4571-4580. doi: 10.2147/RMHP.S335150. PMID: 34795542.
3. Ramtinfar S, Chabok SY, Chari AJ et al. Kidney disease improving global outcome for predicting acute kidney injury in traumatic brain injury patients. *J Acute Med* 2016; 6: 90-94. doi: 10.1016/j.jacme.2016.09.004. PMID: