World Journal of Clinical Cases

Editorial Office

Dear Editor,

We resubmit the paper entitled **" The Cardiorenal Syndrome in patients with acute heart failure: Neutrophil Gelatinase-Associated Lipocalin (NGAL) does not predict Acute Kidney Injury in patients admitted to Coronary Intensive Care Unit "** after revision according to the objections rose by the Reviewer.

Overall, we think that the criticisms were appropriate and constructive, and we hope that our new amended version of the manuscript could be considered suitable for the publication.

In the revised text, changes are marked in red.

Reviewer's comments:

Although the study result is negative that sNGAL does not predict CRS-1; the investigation is worthwhile for clinical practice.

I have several comments:

1. The major concern of the study is that the outcome could be time-varying, patients can experience wax and wane of AKI depending on the fluctuation of sCr and urine output; thus, the best way to handle this situation is using survival model, that AKI is time-to-event outcome.

Thank you for your suggestion. This is a correct observation. Indeed, we monitored sCr all along during the CICU stay, comparing its value with basal sCr to recognize AKI onset, as earlier as possible, and according to references 10.

2. The mortality outcome should also be reported in table because mortality can be a competing risk for AKI, i.e. a patient who died early will have no chance to experience AKI, thus bias the results. I suggest to discuss this limitation and cite some useful reference (Zhang Z. Survival analysis in the

presence of competing risks. Ann Transl Med. 2017;5(3):47. doi:10.21037/atm.2016.08.62; Competing Risks in Epidemiology: Possibilities and Pitfalls PK Andersen et al. Int J Epidemiol 41 (3), 861-70. Jun 2012. PMID 22253319.) for this discussion.

Thank you for your evaluable comment. As suggested, we added data on mortality in table 1 and added the considerations about the possibility that mortality can be a competing risk for AKI. However, our patients presented mild forms of cardiac and renal damage, so mortality rate resulted very low. Then, we think that in our population data on AKI prevalence were not affected by mortality. In any case, we did not include mortality as endpoint, because the type of the study design and the lowest mortality in our population might affect the accuracy of the result.

3. A multivariable model should also explore association of sNGAL and mortality.

As already stated (see the response to comment #2) mortality rate in our population was very low, this is the reason why we did not include mortality in the multivariate model.

4. Because patients were critically ill that managed in ICU, severity scores such as APACHE, SOFA should be reported and adjusted in multivariate model.

This is a correct observation in ICU patients, who often experience severe and complex diseases. However, Italian Coronary Intensive Care Units are subintensive care units, where the admitted patients do not present severe multiorgan failure (e.g. cardiogenic shock or respiratory failure needing Invasive Mechanical Ventilation). In case of worsening, our patients are moved to a multidisciplinary ICU. For this reason, the routine practice of our CICU does not provide for the collection of APACHE III or SAPSII.

5. "Acute cardiorenal syndrome type 1 (CRS-1) is defined by a rapid cardiac function leading to acute kidney injury (AKI). "--should be cardiac dysfunction.

Thank for this observation, we changed as suggested.

6. the KDIGO definition for AKI is influenced by the use of diuretics; you also need to adjust for this confounding.

As suggested, we re-evaluated the use of diuretics in our patients, but we found no impact on AKI prevalence, such as we found no difference in diuretic dosage in CRS-1 vs no CRS-1 patients.

We add these data in Table 1.

Sincerely,

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