Reviewer's report

Title: Proteinuria and hematuria are associated with acute kidney injury and mortality in critically ill patients: a retrospective observational study

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Reviewer: Meghan Sise

Reviewer’s report:

This is a large retrospective observational study of patients admitted to the intensive care unit (ICU) which show that proteinuria and hematuria detected at the time of admission to the ICU increase the risks of AKI and mortality. The study includes a large number of patients; exclusions are few and well reasoned. The methods are well described, including the relative excess risk index (RERI). The authors showed a “dose-dependent” effect of proteinuria and hematuria on the likelihood that AKI is diagnosed and influenced the prediction of mortality at 3 years. There is excellent longitudinal follow-up, with little loss of patient data. The title accurately reflects what their data has shown, that there is an association between proteinuria/hematuria detected at ICU admission with diagnosis of AKI and mortality. The fact that hematuria/proteinuria interact with AKI and increase the predictability of mortality in the AKI model (with an improved AUC) is a novel finding.

Major Compulsory Revisions

1. The issue of causality vs. association needs to be acknowledged. The authors compare their findings to the findings of hematuria as causal in the pathogenesis of warfarin induced nephropathy or the pathologic effects of glomerular hematuria in patients with IgA nephropathy. However, it is unproven in AKI that hematuria is leading to more kidney damage, rather it may just be a sign of kidney damage. In fact, it’s more likely that more severe case of AKI/ATN causes hematuria, which is associated with mortality. For example, the authors state in the discussion “For the first time, the present study demonstrates the effect of hematuria on AKI and mortality in ICU patients.” This statement implies hematuria has causality, however its merely an association in this study and the wording needs to refer to this as an association throughout the text, i.e. In the above sentence rather “For the first time, the present study demonstrates association of hematuria detected on ICU admission with the diagnosis of AKI and mortality in critically ill patients.”

2. The question posed by the authors is not well defined. It is unclear if they are looking for urinary abnormalities (namely hematuria/proteinuria) as a “biomarker” of AKI or whether they are looking at proteinuria/hematuria as a risk factor or causal in the pathway of AKI. They state “we aim to verify whether proteinuria or hematuria increase the risks of AKI”, however the measurements are taken at
ICU admission, likely at the time of the onset of AKI at the time of ICU admission, and there is no way to tell if hematuria/proteinuria precedes AKI or is just a mediator – i.e. Patient has acute tubular necrosis (ATN) and ATN causes hematuria and proteinuria.

3. The discussion focuses on hematuria/proteinuria as a biomarker that can be easily assayed. If it is a biomarker then the appropriate test must be conducted: sensitivity/specificity/positive predicted value/negative predictive value need to be calculated and discussed.

4. The timing of admission to ICU (and measurement of proteinuria/hematuria) and the onset of AKI diagnosis should be reported. It should be reported as mean w standard deviation. It would be helpful to know if most cases were diagnosed early (i.e. at the time of admission to ICU) or if they were delayed. Does the relationship of hematuria/proteinuria change based on the timing of AKI?

5. Table 3 doesn’t actually add to the overall message of the paper. The distinction can be made with a 1-2 sentence explanation in the results rather than dedicate a full figure to it.

6. Lacking from the literature review is a discussion of the known prevalence of hematuria and proteinuria in patients with acute tubular necrosis, which is the etiology of AKI most like to affect the patients in their ICU based sample. The prevalence of hematuria and proteinuria in this setting has been published in the literature and should be discussed.

Minor Essential Revisions
1. It should be stated in the methods that the patients were consecutively recruited if this is indeed the case.

Discretionary Revisions
1. The writing is acceptable, but could be improved in the following places.
   a) The first sentence of the second paragraph of the introduction, which ends with “and so on”, needs to be revised; this term is too casual for a scientific paper.

   b) The second paragraph of the discussion, the sentence “This is mainly because proteinuria has an impact on mortality outcome with a comparable power to smoking” should be re-written, a suggestion being “This is mainly because proteinuria has an impact on mortality, with an effect on mortality similar to smoking.”

**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: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests