Author’s response to reviews

**Title:** Definition of hourly urine output influences reported incidence and staging of acute kidney injury

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**Author’s response to reviews:**

Dr Kashani,

Editor, BMC Nephrology

Dear Dr Kashani,

Please find attached a revised manuscript (BNEP-D-19-00379) that we would like to re-submit to BMC Nephrology. We thank the two reviewers for their helpful comments. We address all individual comments below and hope that the manuscript is now acceptable for publication in BMC Nephrology.

Thank you.

Yours sincerely,

Mark Devonald
Editor Comments:

In this post-hoc analysis of two prospective observational studies focused on post-cardiac surgery population and also ICU population, the investigators assessed the ability for the appropriate classification of acute kidney injury, and its stages using different ways of calculation of oliguria with serum creatinine as the gold standard.

Strengths:

- Important study as identifying the correct way of oliguria determination is critical
- Reasonable flow of their writing
- Appropriate language

Concerns:

- although urine output and serum creatinine in most cases are concordant, there are some previously published studies showed in a considerable patient population there is a discordance between these 2 criteria of acute kidney injury. Urine output and serum creatinine although are used for assessment of kidney function, they may not provide information about the same construct (please see below). While urine output is dependent on GFR, it also is dependent on the tubular function and use of diuretics. Serum creatinine, however, is mainly an indicator of GFR. Therefore, using serum creatinine as gold standard may not be appropriate to assess the ability of urine output in the measurement of kidney function (in this case, the termination of acute kidney injury). We agree that SCr is an imperfect gold standard. Therefore, recommendations include:

1) report the use of diuretics and adjust the models accordingly;

- we have now reported the use of diuretics in the methods section. For the ICU cohort only 3/150 were prescribed diuretics so we have not adjusted any analyses as these do not affect any outcome. For the cardiac surgery cohort, many more were prescribed diuretics but since we have not conducted any logistic regression assessing UO as a predictor of hard outcomes associated with AKI (e.g. mortality, extremely low in cardiac surgery in our study) then there is no need to adjust for use of diuretics (as yes/no) in multivariate analyses (e.g. table 1).
2) as both of the studies that provided samples for this post hoc analysis are focused on acute kidney injury biomarkers, would suggest to use ADQI suggested 2 x 2 table in order to define appropriate reference standard based on the injury.

- the primary purpose of the two studies in question was to investigate the utility of novel urinary biomarkers of AKI. The biomarkers themselves have not yet been validated and remain under investigation so we did not wish to include biomarker data in the current submission.

- In the result section, where authors describe the differences in AKI incidence based on criteria used, they need to add statistical indicators (e.g., p-value, etc.).

- the p-values from chi-squared analysis of the three biomarkers (SCr, UOmean vs UOcons) have been added to this section.

- In the outcome section, authors need to indicate how many patients died in 48-72 hours when they may not have had time to show AKI based on Serum creatinine level. Sensitivity analysis by excluding them may be needed.

- the number of patients dying with the first 72h has now been added to this section. Sensitivity analyses are unaltered for cardiac surgery as no patients died. For ICU, 11 patients died within the first 72h and when these patients were excluded from the main analyses the differences on reported incidences of AKI and statistical effects on hard outcomes according to method of diagnosing AKI were reduced but this was mainly due to reduced sample size – the majority of deaths in ICU occurred from 3 to 30 days (an extra 22/150 patients)

- low urine output does not necessarily indicate low GFR. for example with low effective blood volume and good tubular function low UOP could only mean significant enhancement in proximal tubular function in reabsorption of water and electrolytes while low UOP and poor tubular function may mean low GFR as intended by the authors. So adjusting UOP for indicators of tubular function or tubular injury may provide additional insights.
- We agree with this interesting point but consider the requested analyses to be beyond the scope of the current paper. Various other urinary biomarkers have been proposed as markers of tubular injury (IL-18, KIM-1, NGAL, Nephrocheck) but none has been validated as a marker of tubular function. Unfortunately we would be unable to assay most of these biomarkers at this stage because their sampling and storage requirements are different from those of our novel biomarkers (which are proven to be stable at room temperature).

We have also referenced the following paper that outlines the importance of urine output in ICU (Solomon AW, Kirwan CJ, Alexander ND, Nimako K, Jurukov A, Forth RJ, et al. Urine output on an intensive care unit: case-control study. BMJ. 2010;341:c6761).