Author’s response to reviews

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

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Dr Kashani,
Editor, BMC Nephrology

Please find attached a revised manuscript (BNEP-D-19-00379R1) that we would like to re-submit to BMC Nephrology. We have responded to all individual comments below and hope that our replies are to the satisfaction of the editor and reviewers and that the manuscript is now acceptable for publication in BMC Nephrology.
We look forward to hearing the outcome of the review in due course.

Yours faithfully,

David Gardner and Mark Devonald

Wednesday, 25 September 2019

Editor Comments:

1- diuretic adjustment: You mentioned: "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." This is while a multivariable model for outcome prediction was generated. UOP, of course, did not end up in the model. But the model could be biased as UOP was not adjusted for the use of diuretics. in addition, the UOP is being used to diagnosis and staging AKI. Without considerations that directly impact UOP (including diuretics) the results would be biased.

Thank you for raising this important point. Use of diuretics causes increase in urine output that could confound outcomes (incidence and staging of AKI) when using urine output as an indicator of AKI. We acknowledge this as a limitation in the text. With respect to the use of UO as a predictor of other outcomes such as mortality, we have not conducted logistic regression as only 5 of 150 patients died in cardiology, meaning any analyses would be meaningless. Nevertheless, in Table 1 we have included an analysis labelled as ‘Model 1’ or ‘Model 2’, the latter differing by inclusion of diuretic use (high in cardiology) on the 3 modes of classifying AKI (hence 2 degrees of freedom).

2- Please add a statement in the limitation section or discussion regarding not using injury or functional biomarkers of tubules for validation of your finding.
The following statement has been added in the limitations section: “By design, we have not compared our results with markers of tubular injury or function as ‘biomarkers of AKI’ since these have only been validated in certain clinical settings and are not in routine use.

3- Mortality in the first 72 hours: about one-third of those who died may not have had a chance even to develop AKI defined based on serum creatinine while they actually had AKI. While, reduction in AKI as you mentioned in the revision statements, dismissing this fact just based on the decline in sample size may not provide accurate view of the reality. Therefore, the results of this sensitivity analysis should be included in the result section with added paragraph in the discussion section to describe your hypothesis regarding the observed differences.

No alteration has been made for the cardiac surgery group because so few died. In ICU, 11 of 150 (7%) died within 3 days, which in our ICU would have allowed time for them to be classified as AKI via change in SCr. We suggest that exclusion of these 7% patients from the cohort will not have any significant effect on the sensitivity and specificity analyses.

4- You have not provided point-by-point answers to the comments of Reviewer #2. This is with the recognition that some of the reviewer concerns were addressed in response to the editor's comments. However, we still need point-by-point response from the authors. Please make appropriate changes and resubmit your revised version. Here they are:

We apologise for this omission. Please find point by point answers to referee 2 below

Reviewer reports:

Reviewer #2: The study determines the validity of UO as a screening test for AKI. It compares UO consecutive, and UO mean against the gold standard test. The study noted a variation in the UO consecutive and UO mean in the diagnosis and staging of AKI. The value of UO as a screening measure for AKI is in current debates, and thus the study is timely. However, addressing a few areas would improve the study.

1) Study objectives and hypothesis are not mentioned clearly.
We have tried to make the study objectives clear

2) An explanation of what post-hoc analysis meant would have helped.

Throughout the manuscript we have changed the word ‘post-hoc’ to ‘retrospective’, in that this was a retrospective analysis of data collected for a different reason but was amenable to this type of detailed analysis.

3) The number of deaths among ICU patients is not mentioned.

This has now been added to the results section (page 8). In ICU, 11/150 patients died within 72 hours, 33/150 patients had died within 30 days and 39/150 had died within 1 year. In cardiac surgery, 0/150 died within 72 hours, 5/150 patients had died within 30 days, with no further increase in mortality at 1 year.

4) UO is measured more precisely among patients with a catheter. It was not clear if all the patients in the study were catheterized. If not, then research indicates that UO is usually manually, which can result in clerical errors. This could be added as a study limitation.

All patients are catheterised, and this has now been added to the methods section (page 5). Since all patients were catheterised, UO could be measured hourly for up to 48 hours (or until death/discharge) and SCr was recorded daily for 5 days.

5) The study focuses on comparing UO as a screening test. The authors do not give a rationale for using the logistic regression analysis for the clinical outcomes including mortality. The information about the factors the logistic regression model was adjusted for would have helped. Also, Adjusted ORs for all the factors included in Table 1 would have helped readers in understanding how the Adjusted ORs vary for the other factors.
The rationale for using logistic regression in ICU is now outlined in methods and in relevant legends where the data are reported, such as Table 1. The ability of UO to predict clinical outcomes was assessed by logistic regression in the ICU group alone, due to higher mortality in this group compared with cardiac surgery. In ICU, 11/150 patients died within 72 hours, 33/150 patients had died within 30 days and 39/150 had died within 1 year. In cardiac surgery, 0/150 died within 72 hours, 5/150 patients had died within 30 days, with no further increase in mortality at 1 year. In univariate models, age was found to be a significant predictor of mortality with presence of diabetes also having a weak confounding effect (P=0.10). Age and diabetes status were thus retained in a multivariate model to assess the predictive ability of UO for mortality (Table 1). For both unadjusted and fully-adjusted models, SCr alone was the only significant predictor of mortality for patients admitted to ICU (Table 1).

6) Accuracy and ROC curve should also be presented along with the sensitivity and specificity and Negative and positive predictive values.

95% CI intervals have now been added to Table 3


The reference has been added to the introduction (ref 11 on page 3)