Author's response to reviews

Title: What is the real impact of acute kidney injury? Outcomes in a typical general hospital setting. A retrospective observational database study

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Author's response to reviews: see over
Dear Dr Moranne,

Thank you for asking us to re-submit our manuscript following the reviewers’ comments and suggestions.

We believe we have addressed all of their queries. Below we have documented each of the queries and written a response to each in turn.

If you have any questions or further queries then please do not hesitate to contact us.

Thank you again for giving this article your consideration.

Yours Sincerely,

Michael Bedford  Paul Stevens  Toby Wheeler  Chris Farmer
Reviewer: Catriona Shaw

Reviewer's report:

Bedford et al for BMC Nephrology

Thank you for asking me to review this interesting and informative paper. This paper addresses an important area in helping more clearly understand epidemiology and outcomes associated with AKI in the secondary care setting.

Summary of the paper

Bedford et al present findings from a population based study using data from linked hospital routine data including admission information, demographics, laboratory data, renal unit and ITU data in East Kent. Patients admitted to any of three hospitals between 1/2/09 and 31/7/09 were included in the analysis and followed up until 31/3/11. Patients on chronic RRT, maternity admissions and day case admissions were excluded.

Incidence and outcomes including mortality, in hospital mortality, LOS and ITU utilisation, re-hospitalisation within 30 days are presented by stage of AKI.

The paper is well written. I have some comments/questions which will potentially be easily addressed by some simple edits to the paper in particular in the definitions of the cohort, case ascertainment and outcomes but as they relate to interpretation of the data I have listed the queries under "major" comments.

As the statistical methods used are quite complex I have suggested a statistician reviews the paper.

Major compulsory revisions

-Time of entry to the cohort: was this the date of admission for the individual, or the date of the AKI (date of the peak creatinine- including for the time updated analyses)? This potentially influences the interpretation of the analyses related to ITU admission and LOS and may raise the possibility of reverse causality. For example, it may be feasible that a patient who has a long LOS, has multiple health issues which increase the risk of AKI at some point in that stay, rather than the AKI event itself being antecedent and directly being associated with increased LOS. This query can be resolved by refining the case/cohort definition provided in the paper.

The time of entry to the cohort was the date of admission. We accept that there is the possibility of reverse causality, in that a patient who has a longer admission has a greater risk exposure to developing AKI and that AKI being detected. However of the 5521 admissions with AKI, 4064 had AKI on admission (73.6%) and so makes this situation less likely. Of 633 admissions with AKIN 3, 531 (83.9%) had AKI on admission.

We have updated this in the methods and results sections of the paper to add further clarity.

-I do not agree with the phrase “fully adjusted” used in relation to the multivariable models (e.g page 9). Although the authors have used a range of co-variables in the analyses we cannot know that there aren’t other confounder variables that have not been taken into
account in the analyses that could explain some of the associations identified. For example, in patients with AKI3, severity of other concurrent multi-organ involvement/failure may explain some of the association with mortality. I would suggest this phrase is changed and a direct reference to the risk of confounding added to the limitations section.

We agree with this statement and have made changes to the manuscript to reflect this, including a comment in the limitations section.

• I think the potential for ascertainment bias needs discussing in relation to ascertainment of the AKI cases. For example, sicker patients may have had more creatinine measures, increasing the probability of detecting AKI.

We have now commented on this in the limitations section.

Minor essential revisions Methods:

• Exposure: There is a clear description of what methods were used for the baseline creatinine, however it is not clearly stated that which creatinine during any inpatient stay (presumably the peak) was used as the measure for comparison to calculate the AKI stage for that admission for an individual. For clarity this would be helpful to add.

This has now been added.

• Outcome: How was mortality ascertained? Was this form a link with ONS? Was data on the outcomes of interest complete (e.g. place of discharge)?

Date of death was extracted from the hospital data warehouse. For in-hospital mortality this was from the admission record, and for death within the community the data warehouse record is updated following notification from primary care. Data on LOS, intensive care LOS, re-admission, and place of discharge were complete, as recorded on the patient administration system (PAS).

We have added this to the manuscript and also added a comment in the limitations section to acknowledge that the place of discharge is dependent on the accuracy of coding.

• Was a competing risks framework used/considered e.g. for the outcome hospital re-admission analyses (all-cause mortality as a competing risk)?

For the re-admission analyses the outcome was a binary variable (re-admission within 30 days – yes/no). It is our understanding that you can only account for competing risks within a survival analysis, or possibly if for example the outcome had been time to re-admission. However the outcome is a binary outcome and therefore we have not used competing risks for this outcome.

• There is an error on page 7 - the text currently reads “there were 20,464 admissions with no AKI and 5,521 admissions with AKI...Of these, 3,961...”. The breakdown (3961 + 1927 + 633) AKIN1-3 totals 6521 not 5521.

On review, this is not an error. The text the reviewer is referring to reads “Of these, 3,961
admissions had AKIN 1, 927 admissions AKIN 2, and 633 admissions AKIN 3”. We think there may be a confusion with the documentation of the 1 being part of AKIN “1” and not being part of the number of patients with AKIN 2 which is 927 and not 1,927.

Results:

• I think it would add additional information and help interpretation of the regression model effect estimates if further descriptive stats were provided (potentially as an on line appendix/ supplement if the word limit is a problem) e.g. baseline eGFR/CKD stage, categories of types of primary admission diagnosis, and place of residence prior to admission, and categories of primary diagnoses as part of the baseline descriptive characteristics.

We have added further descriptives both to the existing demographics table and also an additional table which could be included in the manuscript or online?

Discussion:

• Is there any data which provides validation that the catchment population for this cohort is representative to the rest of England/UK? This would help the reader in terms of the generalizability of the papers findings.

It is true that the catchment population does differ from the rest of England/UK. We have added this to the limitations of the manuscript.

Discretionary revisions: These are mainly stylistic.

• Abstract: I would remove the word “actual” from “actual incidence” in the abstract. As the analysis is conducted using routine care data, not all individuals will be tested equally and this study reports the “detected” AKI incidence in a secondary care population.

We have made this change.

• Consistency between the outcomes reported to have been selected (methods section “outcomes” and also in the stats section of the methods) and those reported (table 4). In addition, the methods section says 3 models will be reported 9 unadjusted etc.), but in table 4, there are 4 models reported. In the results text presentation of the outcomes, as in the order presented in the methods may be neater.

We now only present 3 models as also suggested by reviewer 2.

• Statistical methods: it may improve the flow of the stats methods section to place the sentence “a time dependent risk analysis for survival was employed to allow adjustment for multiple admissions...” is placed after the descriptive statistics section, and next to “.Cox regression was used for...”.

We have made this change.

• Statistical methods: a time updated analysis approach was used with the Cox model for all-
cause mortality and it is stated that within patient correlation was addressed using a random effects approach for the outcome LOS. Re-wording of this paragraph so it is more clear how within patient correlation (if multiple observations per patient were used when available) was managed in the analyses for other outcomes (in patient mortality, re-admission etc) would be helpful for the reader.

•Table 4-if the table needs to go on 2 pages, I suggest that the header for the table columns are inserted on the second page also for ease of reading.

We agree at the time of proofing this would be helpful.

•Table 3- 3 decimal places are probably not needed, 2 would suffice.

We have made this change.

•In the discussion: the authors comment “the incidence of AKI... is significantly higher than previous estimates”. Do the authors have some explanation for why this is the case? Perhaps could this be due to increased testing of creatinine due to increased awareness? Change in definitions with AKIN criteria compared to other studies (they mention that there may some misclassification with cases of progressive CKD)? a true increase? I think their insights would be valuable addition to the discussion and also help the reader think about the generalizability of the findings.

We have added some comments to address this.

•Discussion: The incidence reported here is in secondary care inpatients. A future area of interest would be to additionally try and understand more regarding community based AKI events in individuals who are not admitted to hospital.
Reviewer: Raymond Hsu

Reviewer's report:

This is a somewhat straightforward descriptive study assessing the population incidence of AKI in a defined catchment area in East Kent, United Kingdom. The strengths include the large sample size and seeming completeness of data available to the researchers. However, the findings of this study are not really that novel, and for audience outside of the UK, it's difficult to appreciate what's so innovative about the accurate depiction of AKI incidence in a "district general hospital setting."

Critical comments as follow:

MAJOR COMPULSORY REVISIONS

1. The authors's main goal is to describe the population incidence in this area. They elected to study adult patients only, having excluded patients <18 years from analysis (numerator ascertainment). However, in their calculation of incidence (or more accurately, the incidence rate), they used the total population of East Kent, approximately 720,000, as the denominator. Authors cannot claim that their "per million person-year calculation" is correct if the denominator used is that of the entire population including children. In addition, 720,000 seems a fairly rough estimate. The authors need to cite specific census source(s) for their population counts, and describe whether the census year matched their study year.

We agree this is an error. We have now defined the total population at the time of the study (2009) as 744,400. The adult population (18 years +) was 582,300 (Mid-Year Population Estimates published by the Office for National Statistics (ONS), 30th April 2013).

We have updated the manuscript accordingly.

2. Additionally, for the incidence calculation, the authors should be more transparent in their explanation of how they derived 12,394 pmp/yr. It seems to me that they took 4462 patients that had AKI, multiplied by 2, then divided by the 720,000 population count. First, this method should be spelled out more explicitly in the Methods. Second, the assumption of this method is that the 4462 cases from February through July of 2009 is representative of the whole year, but there may indeed be seasonal variation in the incidence of AKI (ie related to flu season, related time of the year when more pts may undergo surgery, related to skill level of practitioners/trainees). The study would be stronger if authors could conduct the analysis on the entire calendar year so that a more accurate incidence rate can be calculated. If this approach is not do-able, authors should explain why they picked the study period and address the inference of incidence rate from only 6 months of data as a major limitation of the study.

We have now added further details to demonstrate the calculations.
3. If the authors are able to address Comment # 1 above, then it would seem that the calculated incidence would be even greater than 12,394 pmp/yr (ie once they remove patients under 18 from the denominator of 720,000). As they pointed out in the first paragraph of Discussion, the incidence here is "significantly higher than previous estimates." This may be in fact the most novel finding of the entire study, as the regression outcomes showing associations between AKI stage and death, LOS, resource utilization are all very well established already. The authors should expand upon their finding of significantly higher incidence and postulate as to REASONS WHY this may be. Is there something specific about this "district general hospital" setting that is distinctively different from other studies cited, such as the Scottish Grampian region study cited? Or, are we seeing a temporal trend, i.e. incidence has greatly increased since the prior studies? Or, is the increased incidence due to the changing definitions being used? This is really the heart of the paper, and unfortunately the authors currently offer no hypotheses for this interesting finding.

We have corrected the incidence calculations and addressed the reasons for the higher incidence in the manuscript.

4. The use of the lowest serum creatinine in the 12 months following discharge to determine AKI stage (for those without pre-hospitalization creatinine) seems problematic. I am not aware of this method being previously used in other studies. If it has been used, please cite prior example(s). The assumption that AKI must have occurred if serum creatinine improved following admission by greater than 26.4 may not always be correct. For examples, pts may lose great muscle mass during prolonged hospitalizations, leading to decrease in serum creatinine; pts may have undergone a kidney transplant (authors do not mention excluding transplant pts) leading to decline in creatinine; a patient who required dialysis-requiring AKI who subsequently remain dialysis-dependent (or a patient who became dialysis-dependent in the months following discharge) can easily have a lower creatinine than the peak hospital creatinine. I think the study would be stronger if this method was not used altogether. Alternatively, authors can perform sensitivity analysis excluding the number of patients whose AKI was ascertained using the post-discharge creatinine, to see of the incidence changes significantly. (Again, as the authors give no explanation as to why their incidence is so high, I wonder if it is partially due to ascertainment bias here.)

Patients undergoing renal replacement therapy, including both dialysis and renal transplantation have been excluded from this study. We have now made this clearer in the methods description.

The (UK) Renal Association Guidelines (8th March 2011) suggest that a reference serum creatinine value can be estimated from the nadir serum creatinine value if patient recovers from AKI.

http://www.renal.org/guidelines/modules/acute-kidney-injury#sthash.LF5eF8Vm.dpuf

Of 5521 admissions with AKI, 455 (8.2%) involved the calculation of a baseline using the lowest serum creatinine in the 12 months following discharge.

Of the 36,015 admissions, in 4,580 admissions a baseline creatinine from the 12 months following discharge was used. In these 4,580 admissions, 7.2% had AKIN 1, 1.4% AKIN 2.
and 1.3% AKIN 3. This is in comparison to admissions in which a baseline from the 12 months following discharge was not used, in which 11.5% had AKIN 1, 2.7% AKIN 2 and 1.8% AKIN 3.

We have added this to the manuscript and discussed it further in the limitations section of the manuscript.

5. There is a discrepancy between what the authors described as a 3-stage method of regression analysis in Methods and what is presented in the Results (where in Table 4 there appears to be 4 models). It seems that the authors should perform 1) adjusted model, 2) gender & age-adjusted model, 3) gender, age, and "other covariates" (as listed in Table 1, including Charlson co-morbidity Score). The whole point of the Charlson score is to define the burden of baseline conditions, so I don’t see the need to perform a fourth model with the individual co-morbidities.

We agree that we should only present 3 models and have removed the individual co-morbidity model from the manuscript, leaving the multiply adjusted model including the Charlson score.

MINOR ESSENTIAL REVISIONS:

1. In the Data Extraction section of Methods, authors should further define how patients who had AKI and required dialysis are extracted. Authors later describe how RRT was abstracted from the renal data system in Outcomes, but inpatient dialysis for AKI is a main predictor here. Also, would make sure that authors did not only look for dialysis in patients meeting AKIN stage 3 creatinine criteria, as it is very possible a large subset of patients had less substantial delta creatinine before requiring dialysis.

Both RRT recorded on the renal data system or on the ITU data system was extracted for the patient cohort included in the study. This was not just confined to patients meeting the AKIN stage 3 creatinine criteria and in fact the patients who did not meet the AKIN 3 creatinine criteria but received RRT were upgraded to AKIN 3 in line with the AKIN criteria.

2. It is unclear how baseline CKD stage was defined. I am unclear what is the "baseline pathology data" (in Independent Variables, under Methods). Is the CKD stage obtained using the "baseline creatinine" from the same methodology as described in the previous paragraph (under Data Extraction)? Did authors also use the post-discharge nadir creatinine to define CKD for the subset of patients without pre-hospitalization creatinine?

Baseline CKD stage was defined using the baseline creatinine (lowest creatinine in the 12 months prior to admission), or the post-discharge nadir creatinine was used for the subset of patients without a pre-hospitalisation creatinine.

3. In the 3rd paragraph of Results, they write: "Co-morbidity was over represented in patients with AKI, but this was not related to AKI stage...deprivation was not related to AKI stage." These statements imply some sort of trend testing was performed, yet no methods or results of any statistical tests were shown. Looking at Table 2 last two rows, it DOES look
like there is a trend of more co-morbidities with increasing stage of AKI.

For a number of the co-morbidities, a greater proportion of patients with AKI have a specific co-morbidity in comparison to those without AKI, however we do agree that when looking at the Charlson score there does appear to be a trend of increasing co-morbidity with increasing stage of AKI. We have therefore re-worded this in the manuscript.

4. In Table 4, all of the outcomes listed are binomial outcomes (ie Risk of Death, In-Hospital Mortality, Readmission) except Relative Length of Stay and Relative ITU Length of Stay. As the authors provide odds ratios here, I wouldn't really know how to interpret the OR's in those two columns without further explanation.

These are ratios of length of stay of a person with AKIN 1 for example in comparison to a person with no AKI. We have updated the table to clarify this.

DISCRETIONARY REVISIONS:

1. Too many figures/tables. I think Table 1 can be eliminated and placed into the text. In fact, the paper would be stronger if the authors had a separate paragraph in Statistical Methods describing the co-variates used in multivariate regression analysis, and WHY those co-variates were chosen. For example, cite prior literature supporting why you picked Weekend Admission as a factor.

We have now removed table 1 and incorporated this into the text as suggested.

2. Table 2 also contains perhaps some uninformative information. I don’t think it’s necessary to list every single co-morbidity extracted, as these are all presumably code-based. I think showing the Charlson Index scores would be sufficient. If authors wish to keep all the rows, they should explain, for example, what constitutes "Renal Disease" in their data extraction. It may actually be more informative to show the co-variates used for regression analysis (currently listed in Table 1) by AKI stage.

Reviewer 2 has suggested removing some of the co-morbidity, whereas reviewer 1 has suggested increasing the reporting. We would value editorial guidance on this.