Author’s response to reviews

Title: Hospital Acquired Acute Kidney Injury is associated with increased mortality but not increased readmission rates

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Dear Dr Abdel-Kader

We re-submit for your consideration our paper concerned with acute kidney injury (AKI), and the associated mortality both in and out of hospital. Many thanks for your comments which we have addressed as below.
1. The IRB status of the research is a concern. Is there an overarching IRB governing the deidentified data warehouse from which this analysis originates? If not, I believe we will need a determination of IRB exempt status by an oversight body. While I agree based on the authors description that this study would be IRB exempt, this determination (or similar, for example related to QI projects) is still necessary.

   We have discussed this with our Clinical Informatics Department. Data handling and masking of data sets to prevent identification is overseen by NHS-Digital and is fully compliant with regulations in the UK governing the NHS. The study is registered as a clinical audit. We have included the statement below in the declarations section of the paper.

   ‘This study did not require institutional review board approval equivalent because of the pseudonymized nature of the data retrieved. Data was linked by NHS Informatics utilizing specialized Informatics identity codes to create a pseudonymised data set avoiding any patient identifiable data. The NHS Informatics process to undertake this pseudonymisation is reviewed and regularly audited by NHSD (NHS Digital) to ensure compliance with the appropriate governance requirements. This observational study was registered as a clinical audit (audit number CARMS-13574)’

2. Please clarify the term: AKI outside renal services (perhaps, AKI in patients not previously followed by a nephrologist).

   This has been changed

3. Please clarify the term hospital wide. Might this be simply described as hospital acquired AKI (without restrictions or modifiers).

   We have changed this to hospital acquired AKI or where referring to hospital populations have used the term ‘unselected inpatient population’
4. In the abstract, please remove the OR for readmission rates in regards to AKI (further comments below), and simply note that AKI was not associated with readmission. The reported OR suggest a potential protective effect and as the authors note, there are likely biases driving this, which are highlighted in the text but not the abstract.

We have removed these

5. The determination of hospital acquired AKI is a bit problematic. Patients may have community acquired AKI but still not reach peak creat for 24-72hrs after readmission or even longer. Hence the utility of baseline creat as raised by the reviewers. In the absence of baseline data, please perform a sensitivity analysis excluding patients who reached peak creat within 48hrs of admission.

Please report mortality HR associated with AKI (no need for AKI stage subgroups) and readmission HR using cox proportional models adjusting for the confounders included in the current models.

We have performed sensitivity analyses and included in the methods this statement:

‘We performed sensitivity analyses to establish that hazard ratios were not changed if creatinine peaking before 48 hours were excluded, in order to ensure community acquired AKI was not included.’

And in results

‘We performed sensitivity analysis to ensure that HRs were similar for patients when creatinine peaking within 48 hours were excluded, to allow for community acquired AKI to be excluded. HR for inpatient mortality for patients with AKI with peak creatinine more than 48 hours after admission was similar: 1.82 (CI 1.61 - 2.07) and for 90 day mortality for AKI stage (see comparison to Table 3) HR were 1.32 (1.05-1.66) for AKI 1; AKI 2 1.46 (1.03-2.09) and AKI 3 2.21 (1.46-3.33), very similar to the analysis where all creatinine post admission was included’
And for readmission

‘In sensitivity analysis including creatinine before 48 hours of admission, AKI remained an insignificant factor for readmission.’

6. In the methods, please describe the exact criteria used to define AKI, since this is the primary exposure of interest.

We have added exact criteria.

‘Specifically AKI Stage 1 was defined as a serum creatinine increase of 1.5–1.9 times index or ≥0.3 mg/dL; AKI Stage 2 as a serum creatinine increase of 2.0–2.9 times index and AKI Stage 3 as a serum creatinine increase of ≥3.0 times index creatinine or ≥4.0 mg/dL or initiation of RRT.’

7. Similarly, in the methods, please describe how death and rehospitalization were adjudicated (national database, local data captured in EHR, etc). This will make limitations of the study clearer.

We have described this: ‘Readmission data was extracted from the hospital systems (from Lorenzo, the Patient Administration System) by the Informatics department, this data is used to report hospital activity nationally. Data on patient death was extracted from the NHS Spine (national death files), also via informatics.’

8. Similarly, for CRP, please describe how it was stratified (deciles, a priori cut offs based on prior literature).
The decision to stratify CRP in this way was initially based on prior clinical consensus. Since the lowest AKI event rate per stratum is >60 (>2.5% of events), and the lowest number per stratum was >1400 (at 90-100) (>1.25% of admission); all p values were less than 0.001 and the effect of CRP was progressive (both with respect to AKI risk and mortality), we feel that the precise way in which CRP is stratified is not a plausible source of error.

This stratification is the same as that published previously by our group in Nephron therefore for consistency it would seem reasonable to maintain the same approach. A similar pragmatic approach is taken in previous literature such as: C-Reactive Protein Is an Independent Predictor of Severity in Community-acquired Pneumonia; James D. Chalmers, MBChB, MRCP (UK), Aran Singanayagam, MBChB, Adam T. Hill, MD, FRCPE; American Journal of Medicine.

Finally as regards CRP, previous comments suggested the tables were too long and not all the deciles of CRP should be included, thus some of these were removed. We wonder if this is now the source of some confusion and thus have included all the CRP groups for clarity – this shows clearly the progression of risk across the groups. Should the editor wish to exclude some of the CRP groups we are happy for any to be excluded that are not deemed to add meaning.

We have added to the methods: ‘CRP was stratified in deciles to 100 mg/dL after which it was stratified in 50mg/dL up to 400mg/dL, based on prior clinic consensus and previous data published from our group. This ensured adequate event rates and numbers of patients per stratum.’ We have referenced the previous paper and the prior literature.

Also, please include CRP in table 1 along with a clear description of N with measurement.

We have included an extra row in Table 1 with the number of patients in each who had CRP measured and the percentage of each group this represents.

9. For sepsis, please clarify how this was defined (e.g., 1 code for cystitis met the sepsis definition) or remove references to sepsis and use infections/composite of infections. I believe this is what is shown in Table 3 and 5 with composite infection variable.
We have removed the term ‘sepsis’ from and used ‘composite of infection’ where this was used to define infection from a series of combined codes (referenced as before in the appendix)

10. In the results, the crude mortality rates for AKI I, 2, 3 are reported in passing (and surprisingly show lower mortality with more severe AKI). However, the adjusted analyses do not show this. Please make comment in the results re: the adjusted mortality HR by AKI stage are shown in (table xyz) or remove the unadjusted rates which could be misleading when read.

We have removed the crude mortality rates for AKI by stage.

11. The primary analysis for mortality and rehospitalization should be an adjusted cox proportional hazards model (i.e., time to event analysis). Whenever this is feasible, there is no need for a logistic regression analysis to supplement this and those analyses can be removed.

We had originally performed logistic regression because these analyses make less assumptions. In view of these comments we have also performed cox regression analyses for all previous logistic regression analyses and replaced the tables accordingly (Tables 2, 3 and 4 (was originally table 5)) and additional files 4 and 8 (originally 12)) and replaced all refernces to logistic regression in the text.

12. Please move table 4 to the supplement.

This has been removed and submitted as supplementary material.

Please drop p-values from table 5.
These have been deleted but this table has been changed to cox regression (with P-values deleted, this can be reversed if we have interpreted this instruction wrongly – we have left them available if needed).

13. For figure 1, please incorporate how many patients died as the hospitalization #'s are otherwise misleading.

This has been inserted into figure 1

14. Please remove additional files 8-11 as well as 13 (as presented in the revised version's additional supplementary uploaded files).

These have been removed and the numbers of these files adjusted in the text.

Please ensure data re: logistic regression is reported as OR, CPH regression as HR (rather than coefficients/betas which are difficult for readers to interpret).

We have changed all the tables to reflect this.

15. For all regression analyses, please place the specific variables that were including for adjustment in the caption (e.g., adjusted for age, gender, race, DM, HTN, HF, etc).

We have added all the variables into the captions.
16. In the limitations, would include selection bias related to the exclusion of patients under nephrology care. Because CKD is a significant risk factor for AKI and patients who are sicker are generally more likely to be referred, exclusion of these patients may have excluded some of the patients with heavier comorbidity burdens who could have been more likely to die or be readmitted after an AKI.

We have included this statement in the discussion ‘CKD is a significant risk factor for AKI and patients who are sicker therefore be under nephrology and excluded from this analysis. This may result in fewer patients in this study with heavy comorbidity burdens, who may have been more likely to die or be readmitted after an AKI.’

17. Please clarify the sentence "AKI is an independent... first two periods." The periods being referenced are ambiguous.

We have clarified this ‘AKI is an independent risk factor in hospital and up to 90 days post discharge …’

Reviewer reports:

Chethan Puttarajappa (Reviewer 2): Thank you for responding to the questions/suggestions.

Recommend making the following changes/modifications in addition.

- Newly added Figure 1: there is an error in the final patients with no AKI group. The number does not add up

We have corrected this.
-Baseline characteristics: Since crp is one of the main variables of interest in the paper, it is necessary to have the average values in the respective groups. Since the authors have also given us multiple ORs for different levels of crp (I am not sure if this is necessary), it will be nice to know the actual distribution of crp among the study population (both in the cases and controls).

We have added numbers of patients who had CRP taken and average CRP in each of the three groups in table 1 (whole population, no-AKI and AKI- CRP is taken more frequently and is higher in the AKI population)

-please elaborate a bit more about the the choice of co-morbidities in the logistic reg model (are the comorbidities listed in the Tables the only ones used in the model).

We have added explicitly in the methods the comorbidities tested in the models.

Also, I would also provide univariable analysis results (either in the main document or in the supplement) since it will be interesting to know how much the effect of crp varied on the univariable and multivariable analysis (which included infection, cancer etc that are associated with high crp)

We have included as supplementary material univariable analysis for CRP for inpatient mortality (and multivariable only including AKI); univariable analysis for CRP for mortality at 90 days (and multivariable only including AKI); univariable analysis for CRP for mortality beyond 90 days (and multivariable only including AKI).

We have referenced this analysis in the methods:

‘Univariate analysis were also performed for CRP alone for mortality in hospital, at ninety days and at the end of follow up and these were additionally performed with AKI as the single multivariate factor with CRP.’
And in the results:

‘CRP as a single variable and as a variable with only AKI were also examined. CRP was a significant predictor of death at all time points (see also additional file 11)’

I hope these changes are satisfactory.

Yours sincerely

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