**Author's response to reviews**

**Title:** A comparison of CKD-EPI estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations.

**Authors:**

Andrew A Udy (andrew_udy@health.qld.gov.au)
Fraser JA Morton (fraser_morton@health.qld.gov.au)
Sallyanne Nguyen-Pham (sallyanne.nguyenpham@uqconnect.edu.au)
Paul Jarrett (paul_jarrett@health.qld.gov.au)
Melissa Lassig-Smith (melissa_lassig-smith@health.qld.gov.au)
Janine Stuart (janine_stuart@health.qld.gov.au)
Rachel Dunlop (rachel_dunlop@health.qld.gov.au)
Therese Starr (therese_starr@health.qld.gov.au)
Robert J Boots (r.boots@uq.edu.au)
Jeffrey Lipman (j.lipman@uq.edu.au)

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**Author's response to reviews:** see over
Dear Dr. Weisbord,

RE: MS1093060563103340; A comparison of CKD-EPI estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations.

Thank-you for the opportunity to respond to the reviewers’ comments, overall we have found them to be highly constructive. Please find below a point-by-point reply to each of the issues raised, in addition to a revised manuscript attached. For convenience, all changes have been annotated in red.

Once again, we appreciate the opportunity to submit this work to BMC Nephrology. Please do not hesitate to contact me if anything further is required.

Kindest regards,

Dr. Andrew Udy

REVIEWER ONE:

In this article, the authors proposed to compare commonly used estimations of GFR with the “gold standard” 8 hour creatinine clearance in patients admitted to an ICU with normal renal function. The overall message of this paper is that in patients with normal/increased GFR, CKD-Epi and MDRD tend to underestimate GFR while in patients with a measured creatinine clearance of <60 ml/min/1.73m2 estimating equations tend to overestimate GFR. They therefore recommended that these equations not be used in patients in the ICU setting. There are a number of important issues with the interpretation of the results of this study.

Major Compulsory Review Issues:
1. In this study, patients with a normal creatinine on admission were selected. The creatinine was measured using the modified Jaffé method meaning that it was IDMS traceable. In patients with normal renal function, the creatinine clearance overestimates GFR by approximately 20% because of tubular creatinine secretion. Before the advent of IDMS-traceable serum creatinine assays, this was counteracted by the approximately 20% overestimation in serum creatinine because of the presence of other chromagens in the serum. However, now that these modern assays are in common use, measured creatinine clearance tends to overestimate GFR by approximately 20% in...
patients with normal renal function and more in patients with stable CKD (up to 50% of creatinine excretion is via tubular secretion in patients with advanced CKD). This is almost exactly the difference between the CKD-Epi estimated GFR and the measured creatinine clearance in patients with eGFR>90 ml/min/1.73m2. This is elegantly demonstrated in figure 3. Thus, the conclusion that the CKD-EPI equation significantly underestimates GFR in this population is not supported by the data as presented.

REPLY: Thank-you for this observation, we would agree with the reviewer that there have been significant improvements in creatinine measurement over-time. We would also agree that the use of endogenous creatinine clearance (CLCR) as a comparator is confounded by tubular creatinine secretion. However, our rationale in using this variable in analysis is based on its’ use as a modifier of drug dosing. In particular recent research has identified threshold values associated with sub-therapeutic drug concentrations and worse clinical outcomes. We have altered the discussion to include the inherent limitations of using a measured CLCR, and to illustrate that this analysis represents a comparison of CKD-EPI eGFR and measured CLCR only. We acknowledge that without an exogenous measure, it remains uncertain whether either estimate is in fact representative of the ‘true GFR’.

2. Of the 28 patients in the CrCl <90 group, 10 had a measured creatinine clearance of <60. This lead to an overestimation of GFR using the CKD-Epi equation. There is no information given on follow-up creatinines (24-48 hours later) in these patients. One major problem with the use of estimating equations in the ICU setting that is well recognized is that creatinine rises late in the course of AKI. As a result, in the setting of a changing serum creatinine concentration, estimating equations tend to significantly overestimate GFR. It would be important to know if any of these patients developed clinically significant AKI during their hospital stay as this may account for the bias noted in the low CrCl group (early AKI with a decrease in creatinine excretion prior to a significant increase in serum creatinine).

REPLY: Plasma creatinine concentrations (CR) were available the following day in ICU for 80 patients (see Table 2). These were not statistically different (P=0.157). Of those with a CLCR < 90, 22 (of 28) patients had a second CR measurement; mean (SD) 67 (21) umol/L. Using a paired-students T-test, there was no statistically significant difference between day 1 and day 2 (p=0.190, n=22) in this sub-group.

3. Given that the study was supposed to include only patients with normal kidney function, would it not be better to exclude those patients with a creatinine clearance <60 from the analysis for the reasons detailed above?

REPLY: We would favor keeping these patients in the analysis, as renal function (determined by measured 8-hr CLCR and CKD-EPI eGFR) was the primary outcome of interest, rather than an inclusion criterion. Our aim was to compare these methods in a cohort of recently admitted critically ill patients with ‘normal’ creatinine concentrations. The observation that some patients had unexpectedly

4. Table 3 appears to be superfluous

REPLY: Thank-you for this observation. This table was incorrectly referenced in the text, which has been amended. These data do however demonstrate variable correlation, bias and precision between CLCR and mathematical estimates in different patient groups. Perhaps not surprisingly, bias is least in the elective admission group, where less physiological disturbance is likely. Consistent with previous literature, bias appeared greater in emergent surgical and trauma admissions.

5. The authors are certainly correct that estimating equations should be used with caution in ICU patients but this is largely due to overestimation rather than underestimation resulting from the lag in increase in serum creatinine in patients with AKI. The reported proportion of patients with augmented renal clearance is likely an overestimation due to the use of the IDMS-traceable standard for creatinine measurement. However, this is not to say that an elevated “creatinine clearance” is not important in these patients given that most drug dosing is based on this measure rather than GFR – but this addresses a different issue (as elegantly demonstrated by these authors in other work) and does not speak to the question of which method more accurately estimates GFR.

REPLY: Please see the reply to point number 1. We would agree with the reviewer entirely; CLCR is an established covariate in predicting drug elimination for renally cleared agents. However, given the widespread automated reporting of CKD-EPI eGFR, use of more established estimates (such as Cockcroft-Gault CLCR or a measured CLCR) is likely to be less frequent. This analysis simply serves to remind the clinician that significant discrepancy exists between these measures, such that triggers for dose modification are not simply transferrable. Which value is closer to the ‘true GFR’ remains untested in this analysis, a point we have expanded on in the discussion. However, as suggested by the reviewer, there is a growing body of literature documenting altered drug pharmacokinetics in association with an elevated CLCR, where as such data are lacking with CKD-EPI eGFR estimates. Additional research is clearly warranted.

6. The statement “While a measured 8-hr CLCR may not be considered a ‘gold standard’ measure of GFR, the application of specific filtration markers (such as inulin) is impractical in the ICU, and tubular creatinine secretion is unlikely to confound the results at higher filtration rates” is not supported by reference 32 which clearly states that creatinine clearance tends to overestimate GFR.

REPLY: This statement and reference has been removed. Please see the revised text.
REVIEWER TWO:

This is an interesting paper looking at the use of CKD-EPI in critically ill patients with presumed normal renal function. Over 100 patients were recruited and the target population was patients with normal serum creatinine concentrations and presumed normal renal function. The equation is compared with creatinine clearance measured over 8 hours. The authors conclude that CKD-EPI is not suitable for use in these patients and suggest that more creatinine clearance measurements should be done.

Major compulsory revisions
1. The limitations of 8 hour creatinine clearance as a comparator need be much more detailed. There are major problems with the use of creatinine clearances in patients with critical illness and this need to be better described.

REPLY: Please see the reply to Reviewer One, Point 1. We have altered the discussion to more thoroughly define these issues.

2. Based on the 8 hour CrCl the authors have concluded that 48% of patients manifested augmented renal clearance. Although I agree this may be a useful construct, particularly when considering pharmacokinetics in critical illness, I suggest that augmented renal clearance and its clinical significance remain uncertain. Some of the limiting features of the 8 hour CrCl may falsely augment the value determined. This needs to be considered as a possible interpretation of the results.

REPLY: Thank-you for this comment. We would agree with the reviewer that ARC remains an evolving concept in critical care research. Although outcome data have been published (Claus BO et al. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 2013; 28:695-700), such findings remain untested in a larger multicenter fashion. In addition, while endogenous CLCR may certainly result in systematically higher values, useful thresholds have been established linked to sub-therapeutic antibacterial concentrations (Udy AA et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 2012, 142(1):30-39). Although such data requires substantial validation, the current analysis reinforces that triggers for dose adjustment are not simply transferable when using variable estimates of GFR in the ICU. Please see the revised discussion.

3. These patients were recruited on admission to the intensive care. What mechanism of altered renal function accounts for the ARC in the early stages of critical illness?

REPLY: This remains an area of ongoing research. Whether this represents an increase in filtration, altered tubular function, or both, has yet to be elucidated. Macrovascular alterations (eg. a raised cardiac output) in association with systemic inflammation are well documented in the critically ill, such that increased ‘solute delivery’ represents an attractive hypothesis. However, changes at a
Recent data from Shimamoto et al. (Intensive Care Med. 2013 Jul;39(7):1247-52) elegantly illustrates the role of systemic inflammation. Here an increasing number of SIRS criteria was associated with augmented drug clearance in those receiving vancomycin, which was most pronounced in younger patients. Unfortunately with our current study dataset we are not able to explore such variables in greater detail.

4. Could the ARC be a manifestation of mathematical error caused by inaccuracies in the assays for serum and urine creatinine?

REPLY: Conceptually this would seem unlikely, as ARC has been demonstrated to occur with other renally excreted solute, such as aminoglycosides (Conil JM et al. Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int J Antimicrob Agents, 2006; 28: 226-230), beta-lactams (Roberts JA et al. Piperacillin penetration into tissue of critically ill patients with sepsis--bolus versus continuous administration? Crit Care Med, 2009; 37: 926-933), low molecular weight heparins (Robinson S et al. Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial. Crit Care, 2010; 14(2):R41), and glycopeptides (Barbot A et al. Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med, 2003; 29: 1528-1534). The association between elevated drug clearance and augmented CLCR suggests the latter may be a useful screening tool, allowing the identification of patients at-risk of under-dosing. No data currently exists for CKD-EPI estimates in this regard.

5. The secretion of creatinine in may be markedly altered in critically ill patients, perhaps affecting even the higher creatinine clearance calculations? What data is there to support the presumption it does not affect the calculation in this group of patients?

REPLY: This remains an area of ongoing research, as to our knowledge, there are no published data addressing this question. We have amended the discussion in the manuscript to reflect the potential confounding influence of CR tubular secretion on the results.

6. What was the effect of diuretics (frusemide or mannitol) on the measurements?

REPLY: Only four patients received mannitol administration, making any further interpretation difficult. The following table provides measured CLCR, CKD-EPI, 175 MDRD and CG CLCR values in those receiving frusemide compared to the remaining cohort.

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<th>Mean (SD)</th>
<th>r (p-value)**</th>
<th>Bias +/- Precision</th>
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<tbody>
<tr>
<td>Frusemide (n=13)</td>
<td></td>
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<tr>
<td>- Plasma Cr</td>
<td>77.9 (27.7)</td>
<td></td>
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<tr>
<td>- CLCR</td>
<td>74.3 (32.8)</td>
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These data suggest an association between frusemide administration and depressed renal function, regardless of the assessment tool. It remains uncertain whether this reflects over aggressive attempts a fluid diuresis, or clinician directed therapy in the face of oliguria. Of note, although the plasma creatinine concentrations were higher in the 'Frusemide' group, this was not statistically significant. Bias was significantly higher in the 'No Frusemide' group, consistent with the findings in patients with a CLCR > 120ml/min/1.73m². These data could be added to the paper, although it is not felt that they add substantially to the analysis.

7. Unfortunately there remains no ‘gold standard’ for measuring GFR in AKI (or indeed in this case critical illness) and conclusions need to reflect this.

REPLY: We would agree with the reviewer entirely. The manuscript has been altered accordingly.

8. The conclusion that measured CrCl should be used has not been proven; only that CKD-EPI does not perform well when measured against it.

REPLY: Thank-you for this comment. We have amended the manuscript as suggested.

Discretionary Revisions
1. In table 2; I am uncertain that listing the mean urine output, urinary creatinine and fluid balances for the whole cohort of patients contribute to our understanding of the data to the information

REPLY: As suggested, these have been removed from the table.