Author’s response to reviews

Title: Prognostic robustness of serum creatinine based AKI definitions in patients with sepsis: a prospective cohort study.

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Author’s response to reviews: see over
Reviewer's report

Title: Prognostic robustness of serum creatinine based AKI definitions in patients with sepsis: a prospective cohort study.

Version: 1

Date: 29 May 2015

Reviewer: Zhongqing Chen

Reviewer's report:
First I'd like to compliment Dr Biesen and his colleagues about their work on exploring the conventional sCr on the diagnosis of AKI in patients of sepsis. The authors performed a very interesting study aiming to evaluate the influences of three sCr increase algorithms including #HIS, #EST, #ADM, on the prognostic value of AKI for prediction of mortality in patients with sepsis. This is a nice study and would appear to add to the existing literature on sepsis-AKI.

A few comments /queries for the authors to address:

Comment 1: #HIS and #EST used the highest value in the first 24 hours after ICU admission; however, the frequency of blood samples obtained was not mentioned in the paper. How often was sCr measured?

Answer: Serum creatinine was measured at study inclusion (D0T0), four hours later (D0T4) and at 6AM the day following study inclusion (D1). There was also an ICU admission serum creatinine value available for all patients, independent of the study protocol. The text has been changed accordingly in the methods’ section. (see page 8, second paragraph)

Comment 2 In the methods section, the authors mention that “All sepsis patients admitted to ICU between 6 AM and 18 PM...as that used to calculate #HIS and #EST (page 8)”, however, the Figure 1 was hard to understand: the first samples of “the sCr value ICU adm” were both obtained at 18:00. I am interested that how obtained the samples from the patients of part A (admitted just after 18 pm) at 18:00 p.m. and why obtained the samples from the patients of part B (admitted just before 18 pm) postponed to 18:00 p.m...

Answer: JV daily screened ICU patients for eligibility between 6AM and 18PM. In case eligible patients were admitted after 18PM, they were included the next morning at 6AM (patients could only be included during working hours ((6AM-18PM), Monday till Sunday). This means that all patients were included in the study between 0h and 12h after ICU admission. All patients had a measurement of serum creatinine at ICU admission value (independent of study protocol, but standard care in our hospital). According to study protocol, serum creatinine values were measured at study inclusion (between 0 and 12h after ICU admission), 4 hours later and at 6AM the day after inclusion (=D1 value). So
theoretically the time interval between the first blood sample at ICU admission (independent of the study protocol) and the ‘D1 value’ might not exactly be 24 hours. We agree with the reviewer that this was not well explained in the text and thus we have adapted this paragraph. (see p8-9)

Comment 3: Still in the methods section, I understand why the authors adjusted for the “24 hours” fluid balance. However, in the study, the authors mention that: “The mean time interval between D1 and ICU admission in our cohort was 26 hours (page 8)”. I believe that the time of duration of clinical intervention can affect the sCr values. Why not adjusted for the time interval between D1 and ICU adm?

Answer: We do agree with the reviewer that this varying time interval between D1 and ICU admission between patients could provoke a problem if we would be evaluating the epidemiology of septic AKI. However, since we were interested in studying the effect of using different algorithms to calculate serum creatinine increase and because there was no difference in the applied time interval for the three algorithms within one patient (for each patient the time interval used for \( \Delta \)HIS, \( \Delta \)EST and \( \Delta \)ADM was the same), we do not think this is likely to have influenced our results. The time interval only varies between patients but not within one individual patient. Additionally the mean time interval between the value at D1 and ICU admission was 26h which approximates 24h. Also, if anything, having to deal with varying time intervals between patients would have lowered our chances of demonstrating that including the evolution of serum creatinine in the definition enhances the predictive performance of the label ‘AKI’, since those patients with a time interval less than 24h between D1 and ICU admission are at risk for not being exposed to a sufficiently long observation period to be able to respond positively to fluid resuscitation. However, as suggested by the reviewer we added the total hours of each time interval to the model, which did not change our findings.

Comment 4: I think it will be more clear if some parameters are present as (n, %) (e.g. Ventilation, CKD, RRT need…) in Table 1.

Answer: We agree. This has been changed in Table 1.

Comment 5: Abstract is somewhat too long. Please consider deleting some redundant sentences. E.g.: Methods: Twenty-four hours fluid balance was…; Results: After adjusting for severity of illness…

Answer: We agree. These sentences have been deleted in the abstract.

Comment 6. If abbreviations are used in the text they should be defined in the text at first use.

Abstract /Background section: ICU;
Background section: AKIN, KDIGO, ERBP; Methods section: APACHE II; …
Answer: Abbreviations are now defined in the text where they appear first.
Comment 7. Some labels of reference were incorrect.
[25] [26] [27] [28,29]: Should be revised as [25-29]? (Page 16) [1-4,30,31][32]:Should be revised as [1-4,30-32]? (Page 16)

Comment 8. I have a major concern regarding clinical registration. This is a clinical study being performed in 2010-2011, but I cannot find any registration information in the manuscript.

Answer: We can only agree with the reviewer that from a methodological point of view, it would have been better to register the study. Unfortunately this was not done. The study was approved by the ethical committee of the Ghent University hospital and was registered for a different analysis, namely the use of biomarkers for prediction of AKI. (see clinicaltrials.gov NCT01981993)

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests
Reviewer's report

Title: Prognostic robustness of serum creatinine based AKI definitions in patients with sepsis: a prospective cohort study.

Version: 1

Date: 1 June 2015

Reviewer: Anne-Cornelie de Pont

Reviewer's report:
In this interesting paper, Vanmassenhove and colleagues analyzed the prognostic robustness of serum creatinine based definitions of acute kidney injury (AKI) in 195 consecutive patients with sepsis.

Major compulsory revisions:

Comment 1: The authors should formulate a hypothesis in their introduction.
Answer: We agree with the reviewer that the hypothesis has not been appropriately formulated and the paragraph dealing with this issue has now been adapted accordingly. (see page 5-6) We hypothesized that using different algorithms to calculate serum creatinine increase would have an impact on the predictive performance of the label ‘AKI’. Additionally we wanted to evaluate the robustness of the association of a 0.3 mg/dl increase in serum creatinine with mortality, in exclusively sepsis patients.

Comment 2: Why did the authors choose for mortality at 3 months, 1 year and 2 years instead of the more commonly used 28-day, 60-day and 90-day mortality?
Answer: We looked at 3 months, 1 year and 2 year outcome data because we were interested in both short and median term outcome. The effects of sepsis and septic AKI can expand well beyond 28 days, which also explains why we decided to evaluate outcome at these specific time points. (REF Vincent et al-CCM-2004, Davis et al-Plos One-2014 and Winters et al-CCM-2010)

Comment 3: In this small cohort of patients with sepsis, ICU mortality was relatively low (23%), since overall 28-day mortality due to sepsis is around 30% (Stevenson, Crit Care Med 2014). The authors should comment on this finding.

Answer: As correctly mentioned by the reviewer, in general, ICU mortality rates in sepsis are higher than the rate provided in this study. However, the study of Stevenson et al and several other studies with longitudinal observations have demonstrated that the mortality rate in sepsis is decreasing. (REF Friedman et al-CCM-1998, Martin et al-
NEJM-2003, Gaieski et al-CCM-2013 and Kaukonen-JAMA-2014. In the study by Kaukonen et al the mortality rate in severe sepsis decreased from 35% in 2000 till 18.4% in 2012. (REF Kaukonen-JAMA-2014) In a pan European study, ICU mortality in sepsis was 27%, ranging from 10% in Switzerland to 35% in Italy. (REF Vincent-CCM-2006)

Several studies reporting higher mortality rates include cohorts that are generally sicker or have a higher mean age compared to our cohort. (REF Brun-Buisson-ICM-2004, Vincent-CCM-2006) We did add a paragraph on page 18 where we know clearly state that our results might not be generalizable to other cohorts including patients with different severity of illness.

Comment 4: In a large study among more than 120,000 ICU patients in Australia and New Zealand, AKI was defined by modified RIFLE criteria. Patients with septic AKI had an increased odds ratio for ICU and in hospital mortality when compared with patients with sepsis only (Bagshaw et al, Crit Care 2008). The authors should comment on this study in their discussion.

Answer: In this study by Bagshaw et al, who performed a retrospective interrogation of prospectively included patients, it was indeed found that sepsis, septic AKI and non-septic AKI were all found to be significantly associated with poor outcome. However, authors only looked at short term mortality (28 days and hospital mortality) and no data on RRT need were available, so it is unclear whether the effect on mortality was mainly driven by RRT need. As suggested by the reviewer this study is now discussed in the paper. (see p 16, last paragraph)

Comment 5: In another large multicenter cohort of more than 16,000 ICU patients, the presence of AKI as defined by both the AKIN and RIFLE criteria had an increased odds ratio for hospital mortality (Joannidis, Intensive Care Med 2009). When the creatinine criterion was used alone, less patients were identified as having AKI. It is conceivable that identification of the AKI patients by the creatinine criterion alone occurred later in the AKI process, and that hospital mortality in this group was therefore higher. The authors should also comment on this study in their discussion.

Answer: This is indeed an interesting and relevant comment. In the study of Joannidis et al, mortality risk was lower when based on diuresis alone vs creatinine alone. We agree with the reviewer that using the urinary output criterion allows early intervention (REF Colpaert-CCM-2012), so that outcome is improved. We did similar observations in our cohort of sepsis patients (REF Vanmassenhove-Critical Care-2013).

We have added this now to the discussion on page 19: “Mortality rates in our cohort of patients with sepsis might also be lower than in previous reports because we have a very good system in place in our ICU to alert physicians of pending AKI. Most of these alerts are induced by reduced urinary output (ref Colpaert-CCM-2012). It has been demonstrated before that AKI defined by oliguria has a better prognosis than AKI defined by the creatinine criterion (REF Joannidis-ICM-2009).”
Comment 6: In the current study, the number of patients defined as having AKI by #ADM (n=27) was smaller than when #HIS (n=98) and #EST (n=89) were used. In analogy to the study by Joannidis, this might explain why only the creatinine criterion using #ADM yielded positive odds ratios for mortality. The authors should comment on this.

Answer: It is true that creatinine increase probably comes later in the disease process compared to oliguria. However this would be the same process for all three algorithms (we only used the creatinine criterion) and cannot explain why one algorithm is associated with mortality whereas the other is not. It is likely that by taking into account the evolution of serum creatinine we were able to select those patients with a worse prognosis, which is exactly why the evolution of serum creatinine should be incorporated in currently used AKI diagnostic criteria. The text has been adapted taking into account the remark of the reviewer. (see page 16)

Comment 7: Since the number of patients in the current study was relatively small, subgroup analysis of ICU survivors only is not appropriate.

Answer: Because there is an overwhelming effect of severity of illness on mortality which mainly takes place during ICU stay, we decided to only look at ICU survivors (n=150) when evaluating median term outcome at year 1 and year 2. We agree with the reviewer that this can reduce power and enhance the chances of a type 2 error. However, we feel that this is a clinically relevant outcome measure. Also, this analysis was planned in the original protocol.

Comment 8: Due to the small number of patients, a type II error is not excluded. The authors should comment on this in their discussion.

Answer: We did not perform a power analysis in this observational study applying multivariable analysis and we agree with the reviewer that because of the small cohort there is a chance that our findings are coincidental.

The text was adapted accordingly. (see page 18): “We agree that our results need to be validated in a larger cohort before drawing any definitive conclusion. However, the finding that taking into account the evolution of serum creatinine demonstrates a better association with mortality compared to only relying on a peak serum creatinine value over a certain time span for AKI diagnosis, does make sense from pathophysiological point of view. Taking into account the evolution of serum creatinine allows for the identification of those who have more severe AKI, are more ill and consequently have a worse outcome.”
**Level of interest:** An article whose findings are important to those with closely related research interests. **Quality of written English:** Acceptable. **Statistical review:** No, the manuscript does not need to be seen by a statistician. **Declaration of competing interests:** I declare that I have no competing interests.