Author's response to reviews

Title: Impact of non-dialysis chronic kidney disease on survival in patients with septic shock

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Author's response to reviews: see over
We thank the associate editor for all his/her valuable suggestions and comments.

Editorial request: Please state the specific name and affiliation of the ethics committee that approved the study and add it to the revised manuscript.

As requested we modified the text (page 5 ln 22-23).

Reviewer: Kent Doi

We thank Doctor Kent Doi for all the suggestions and comments.

Reviewer's report:
Slama and colleagues evaluated the impact of non-dialysis chronic kidney disease on septic shock with a cohort of adult ICU. They picked up the patients with septic shock in the ICU whose baseline creatinine are known or whose serum creatinine after admission decreased below the level of eGFR=60 (i.e., non-CKD). The patients with no previously measured baseline creatinine who did not show any lower eGFR below 60 after admission were excluded (n=14). Non-dialysis CKD appears to be an independent risk factor for death, while serum creatinine on admission is not significantly associated with mortality.

Major

1) This study includes non-CKD patients who recovered from AKI, but might exclude non-CKD patients who didn't recover from AKI. I think this could influence results. Because the number of death in this cohort is not so large, mortality of the excluded patients will change the results. Of note, p-values in chi-square test in table 1 are 0.03, which are marginal. At least, the authors should described the mortality of these patients and discuss the potential bias.

Fourteen patients were excluded because it was not possible to determine their baseline eGFR, as a consequence it was not possible to know the proportion of CKD and non CKD patients among them. Among them, 9 (64%) patients died (all during the first the 28 days following the onset of septic shock). Since the proportion of non-CKD in these patients was impossible to determine, it was complicated to include them in the mortality analysis. However and to answer to the Reviewer, we make the hypothesis that all of those patients were belonged to non CKD group, and found only a slight increase in the 28 day mortality rate of this group from 50% to 52%, and the persistence of significant difference between the two groups non CKD and CKD regarding the mortality (p=0.034 instead of 0.029). We now discuss this potential bias in the manuscript (page 11 ln 17-23).

2) This study did not find any significant association between serum creatinine on
admission and mortality. Because it includes ICU-acquired septic shocks, serum creatinine on admission does not always indicate creatinine levels during sepsis. So I am concerned this analysis might not reflect the true association between creatinine and mortality in sepsis. Although ICU-acquired septic shock was not observed frequently (7% of all the examined patients), differences of serum creatinine between ICU admission and at the beginning of septic shock should be evaluated.

We agree with the reviewer. The presentation of the serum creatinine at admission instead of the onset of septic shock could have explained the absence of association with the mortality. Acquired septic shock was defined as shock occurring more than 48 hours after ICU admission. This concerned only 11 (9%) of our total population. However the difference of serum creatinine between the admission and the beginning of the septic shock can also concern the non ICU acquired septic shock patients (modification of the serum creatinine during the first 48 hours in the ICU). We therefore recorded the serum creatinine level for our total population at the onset of the septic shock. The median serum creatinine (µmol/l) at the beginning of the septic shock was 240 (131-390) for all patients: 203 (102-332) in the non-CKD group and 380 (236-469) in the CKD group (p<0.001) (see table 1). The difference between serum creatinine at the onset of septic shock and at admission was not statistically significant. Neither was the creatinine at the onset of septic shock between 28 survivors and non-survivors (see table 2). None of the creatinine at admission or at the onset of septic shock was associated with the mortality (see table 3).

3) This study indicates not the degree of AKI but pre-existing CKD had a significant impact on the mortality of septic shock. What is the possible explanation on this observation? Severity of acute renal insult was evaluated using serum creatinine changes. Reportedly, sepsis will suppress elevation of serum creatinine by reducing the production (J Am Soc Nephrol. 2009 Jun;20(6):1217-21). The authors should address this issue in the discussion.

We now discuss this point referring notably to the study mentioned by the reviewer (page 12 In 3-12).

Minor

4) In the method section of the abstract, 49 patients were described as excluded partly because of missing of baseline eGFR data. Is this correctly reflect the study design? 32 patients without previously measure serum creatinine were included in this study. Although I can understand this after reading all the manuscript, I think this part in the abstract should be fixed.

Accordingly we modified the abstract.
Reviewer: Peter Yuen

We thank Doctor Peter Yuen for all the suggestions and comments.

Reviewer's report:

In this well written retrospective study Maizel J et al. analyzed the impact of non-dialysis chronic kidney disease on survival in patients with septic shock. Although the sample size was small, the study was well conducted. The authors were able to test their hypothesis by using two models to compare survival following septic shock at 28 days and 1 year in patients with and without pre-dialysis chronic kidney disease. The main conclusion of this study is that serum creatinine on admission does not predict mortality, while the Baseline presence of CKD does.

A few concerns/questions should be addressed:

1. In this study only the first incident of septic shock is considered. Is there a difference in the number of septic shock events between the two groups?

During their stay in the ICU, 2 (3.5%) CKD patients experienced more than 1 septic shock vs 9 (8.4%) non CKD patients. This difference was not statistically significant (p=0.34). (page 8 ln 15-17)

2. In a typical backward multivariate Cox Regression analysis all variables are at first included in the analysis and then variables, which do not reach a significance threshold, are successively removed. The methods state that baseline eGFR or CKD status are successively included, which would be more consistent with a forward or stepwise analysis. Please clarify the procedure used for this analysis.

We now have clarified the multivariate regression analysis methodology. (page 7 ln 8-10)

3. What was the average (±error) time between baseline serum creatinine and septic shock onset (more detail beyond < 3 months)?

The median time between the baseline eGFR and the septic shock onset was 22 days (3-73). This delay was calculated considering the time between the last stable serum creatinine value available and the onset of the septic shock. (page 8 In 3-4)

4. When patients did not have baseline eGFR, serum creatinine was collected after the septic shock for eGFR calculation using MDRD. How long after the shock was this creatinine measured and considered for eGFR calculation?

In the group of 32 non-CKD patients for whom the eGFR was determined after the end of the septic shock, the median delay between the end of the septic shock and this determination of the eGFR was 9.5 days (3-18). (page 8 In 4-7)
5. The number of patients with CKD (56) among the 212 patients is already High (34%). When you consider the patients excluded for being on chronic hemodialysis or for past history of kidney transplant, 43% of patients with septic shock have CKD. The prevalence of CKD among patients with septic shock is very high in this study. Although the study of CKD prevalence was not the main goal, it could be briefly discussed in the paper.

We agree with the reviewer and we now emphasize this particularity of our population. This characteristic of our population is probably because our ICU belongs to the nephrology department of our hospital. (page 14 ln 7-11)

6. On page 7 the mortality rates given in brackets are switched with respect to the text. These should be ‘70% vs 50%’ rather than ‘50% vs 70%’.

We modified the text accordingly. (page 8 ln 22-23)

7. Including SAPS II in the models causes other variables to drop below the significance threshold and others to rise above the threshold. This latter change may be unexpected to someone without a firm understanding of statistics. Would including a brief explanation in the discussion be possible?

We included an explanation in the discussion. (page 12 ln 13 – page 13 ln 2)

8. The methods section indicates that all data are expressed as median and interquartile range. Is baseline eGFR presented as mean±S.D in the abstract?

We modified the abstract for median and IQR.

9. As stated the economic burden of sepsis in the United States is nearly $17 billion, but the reference for this figure was published in 2001 and based on data from 1995. Do any subsequent studies have more recent estimates for either the United States or other countries?

According to our knowledge there is no more recent global estimation of the economic burden of sepsis. However recent studies estimate the average per case cost for hospitalization due to severe sepsis in ICU. So we modified our manuscript accordingly. (page 4 ln 4-8)

10. In table 4 Model 2 + SAPS II the text and the values are incorrectly aligned.

The alignment has been corrected (Table 4).