Author's response to reviews

Title: The Ratio of CRP to Prealbumin Levels Predict Mortality in Patients with Hospital-acquired Acute Kidney Injury

Authors:

Qionghong Xie (kionxqh@sohu.com)
Ying Zhou (glorytree@hotmail.com)
Zhongye Xu (lindsay_xu@live.cn)
Yanjiao Yang (yangyanj@126.com)
Dingwei Kuang (dingweikuang@hotmail.com)
Huaizhou You (youhz@sina.com)
Shuai Ma (mashuai0777@qq.com)
Chuanming Hao (chuanminghao@fudan.edu.cn)
Yong Gu (yonggu@vip.163.com)
Shanyan Lin (shanyanlin@gmail.com)
Feng Ding (dingfeng@fudan.edu.cn)

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Dr. Christna Chap, PhD  
Executive Editor  
BioMed Central

Dear Dr. Chap,

Thank you for your review of our manuscript (MS: 1979903784502549) entitled “The Ratio of CRP to Prealbumin Levels Predict Mortality in Patients with Hospital-acquired Acute Kidney Injury”. We are very grateful to all of the three reviewers for their careful reading and thoughtful comments on this study. We have made certain modifications according to their comments in our revised manuscript. Below please find a point-by-point response addressing each of the reviewer’s concerns in detail. We hope the response has adequately addressed the main concerns of the reviewers.

Sincerely yours,

Qionghong Xie  
Feng Ding  
Division of Nephrology  
Huashan Hospital, Fudan University  
12 Wulumuqi Road (middle), Shanghai 200040, China  
Tel: 86-21-52888135
Response to Professor Jose Ramon Perez-Valdivieso:

There are some studies that had reported the relationship between CRP or prealbumin and AKI prognosis before. Does this study show a real novel progress combining CRP and prealbumin in a ratio?

There have been some studies reported that CRP and prealbumin were associated with the prognosis of AKI before. The current study did find that the predictive value for AKI prognosis was improved when CRP and prealbumin were combined. Indeed, neither CRP nor prealbumin was associated with the prognosis after adjusting for SOFA score, probably due to the relatively smaller cohort. Therefore, our study showed that CRP/prealbumin might be a more sensitive predictor for AKI prognosis than either separate parameter.

On the other hand, an adherence to the STROBE statement would strength the study. It is not clear how the cases recruitment was made, or the sources and methods for selection of the controls. Please, describe in deep the randomization procedure. In addition, the small number of patients included could have underpowered the statistical analysis. Furthermore, explain how the study size was arrived at. Again, develop the limitations discussion. Also, it is surprising to find a 74% of males in the population. In larger series studying AKI, the proportion found is about a 60%, so doubts about the external validity of the results could be raised.

We regret not explaining the cases recruitment clearly and have added the following paragraph in the revised manuscript.

In-patient’s serum creatinine data were monitored in our hospital’s information system daily. Patients with creatinine levels rising within one week in accordance with RIFLE criteria were consulted by nephrologists within 24 hours. Those with AKI caused by post-renal obstruction, glomerulonephritis, interstitial nephritis or vasculitis, etc were excluded from the study.

The healthy control was randomly selected in healthcare center of Huashan Hospital, and the stable MHD patients and PD patients were randomly selected from hemodialysis center or peritoneal dialysis center of Huashan Hospital.

About “how the study size was arrived at”.

From previous studies, inflammation and malnutrition might be associated with the prognosis of AKI. The current research is a prospective cohort study designed to analyze the relationship between inflammation or malnutrition and AKI prognosis. The study planed to last 5 years and the data were regularly analyzed. The first year’s statistical analysis indicated that CRP/prealbumin is an independent risk factor for AKI patients while the others are not significantly different after adjusting for the severity of diseases.
About the higher proportion of males than the other studies.

Our AKI population have a higher proportion of males, which coincides with the higher male ratio of in-patients in this hospital. We speculate the possible reasons may include: Huashan Hospital is famous for Neurosurgery and the proportion of patients with brain injuries caused by traffic accidents is relatively high in ICU and males are more likely to have traffic accidents in China. Besides, there are no Gynaecology and Obstetrics department in this hospital.

I think that the results section and the tables could be improved. Please, check and rewrite. This will enhance the manuscript message. It is important to give a clear and concise idea of your work. Add the p value for RIFLE criteria in the univariate analysis.

We must apologize for no p value for RIFLE criteria in the univariate analysis and have added it in the table in the revised manuscript. We have also checked and made some modifications in the results section and the tables in the revised manuscript.

Add more references for the background and method sections, for instance, what are the studies about cholesterol or prealbumin? Give citations for the RIFLE and SOFA scores....

Thanks for your kind suggestions. Researchs investigating the relationships between prealbumin or cholesterol with prognosis in AKI population were not as common as in ESRD patients. We have added several references in the background and method sections according to the suggestions and also added the citations for RIFLE and SOFA scores.

Chertow et al reported that prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. The study by Cano et al showed that an improvement in prealbumin during nutritional therapy was associated with a decrease in morbidity and mortality in malnourished hemodialysis patients. Another study also reported that even though baseline serum prealbumin may not be superior to albumin in predicting mortality in maintenance hemodialysis (MHD) patients, prealbumin concentrations < 20mg/dL were associated with death risk in those patients and a fall in serum prealbumin over 6 month was independently associated with increased death risk. In AKI patients, Perez-Valdivieso et al found that serum prealbumin levels < 11mg/dL were strongly associated with a higher risk of death independent of AKI severity. Besides, few studies reported the predict value of prealbumin in AKI patients. Cholesterol is another nutritional biomarker wildly used in clinic. In 1994, Dunham et al found that patients with severe trauma had a sudden reduction in total serum cholesterol concentration. Hypocholesterolemia has been observed in patients undergoing surgical interventions and in those with multiple-organ dysfunction syndrome. However, few studies showed the association between cholesterol and the prognosis of AKI patients.
In the clinical data section, the explanations about SIRS criteria could be shortened.

We agree with the reviewer’s comments and have shortened the explanations about SIRS criteria.

About the multivariate analysis, why not variables such as mechanic ventilation, or severity of the acute kidney injury were included? It could be argued that patients did worse because of those reasons. This is also a major point that must be clarified.

We totally agree with the reviewer’s opinions. In the multivariate analysis, we have had CRP, prealbumin, albumin, cholesterol or the ratios adjusting for mechanic ventilation, RIFLE, and other parameters which were significantly different between the 2 groups stepwise. The results showed that only CRP/prealbumin was independent predictor for AKI prognosis. The small sample size of the study did not allow to include too many covariates in multivariate analysis. Moreover, SOFA has included score of respiratory system. Therefore, we only show the results adjusted for sepsis and SOFA.

At the same time, I have doubts about the statement that the combined factors were all significantly higher if only a univariate analysis have been done.

Our data did find that all three combined factors were all significantly different in a univariate analysis. Since both CRP and nutrition parameters were associated with AKI prognosis, it is possible to combine them can increased the predictive power further. In multivariate analysis, however, the only significant combined parameter was CRP/prealbumin, even in this relatively small cohort.

The authors should explain why they chose the cut-off value of 0.42 for the ratio CRP/prealbumin. Was it the median, or something else?

The cut-off value of 0.42 was the median of the ratio CRP/prealbumin. We have indicated it in the revised manuscript.

We also used the median of CRP/prealbumin as cut-off point to divide the patients into 2 groups and made the Kaplan-Meier plot (Fig. 2) which showed that the survival of patients with CRP/prealbumin > 0.42 was significantly worse than that of patients with lower levels (log rank test, \( p < 0.01 \)).

About the discussion section, albumin could not be proven to be associated with 90 days mortality after adjusting for model 1 or, on the contrary, table 3 is wrong. Or at least, state if a different p value was accepted in those analyses.

Thanks for reviewer’s careful reading. The result of albumin in our data was different from the previous study and meta analysis. We consider that because the sample size of our study was smaller (n = 155), and we have had some words in discussion section.
Although the phenomenon that the lower albuminemia, the poorer prognosis was also found in our study, there was no statistical significance in univariate analysis ($p = 0.075$). This was probably because the sample size of our study was not large enough.

*I am a bit confused. Is it true that Fiaccadori’s work in 1999 comprises the largest group of AKI patients so far? (discussion section)*

We must apologize for our imprecise narration. There were 309 ARF patients included in Fiaccadori’s study. It was quite a large group of AKI patients at that time. We have modified the statement in the discussion section.

*In Fiaccadori’s study in 1999, severe malnutrition, defined by Subjective Global Assessment (SGA) class C, was documented in about 40% of patients.*

*Unify the term for sex and gender. Choose one or the other.*

We would like to thank the reviewer for noticing the inconsistency in our manuscript. In the revised manuscript, the word “sex” has been globally changed into “gender”.

*Please, provide bibliography to the statement CRP is the best characterized biomarker of inflammation.*

We must apologize for our imprecise statement again. It is inaccurate to say CRP is the best characterized biomarker of inflammation, but it is really one of the widely used biomarkers for monitoring inflammation. And we have modified the statement in the discussion section.

*CRP is one of the widely used biomarkers for monitoring the course of infection and inflammation.*

*Some of the references at pages 16 and 17 look incomplete and should be corrected, e.g. /10, /12, /13; First name, Perez-Valdivieso.*

The reference was obtained on pubmed directly through EndNote. But we still apologize for our mistakes and thanks for the careful reading. It has been revised in the manuscript. Again, we apologize for spelling the reviewer’s first name wrong.
Response to Professor Matthias Girndt:

*The time point of measurement of inflammatory markers is not very well defined. It is related to nephrology consultation. However, this consultation may have occurred earlier or later in the different patients. Do the authors have data on the maximum individual CRP or the lowest albumin during the course of disease? Would this approach change the results? What was the average time between ICU admission and nephrology consultation?*

We regret not explaining the time point of measurement of inflammatory markers accurately. The sample was obtained within 24 hours after AKI diagnosis. And we have revised it in the method section. Although we have observation on the changes of these parameters after one week, only 2 time points’ samples were obtained. So we didn’t have the maximum CRP and the lowest albumin or other parameters during the course of disease. Because we mainly study the patients after AKI diagnosis, we didn’t record the time between ICU admission and nephrology consultation in detail.

The samples for measurement were fasting blood and obtained within 24 hours after AKI diagnosis, predialysis for maintenance hemodialysis patients and random for peritoneal patients and healthy controls.

*Statistical methods should be clarified. The aim of the study (primary endpoint) was 90 day mortality (p.5 last paragraph), however, the results are reported as 28 day mortality (abstract and tables). My understanding is that the study analysed 28d mortality as primary endpoint and reports extended observation in fig. 2, is this correct?*

In our cohort study, Cox regression was used in multivariate analysis and the observational endpoint was the survival status of the patients. In table 1, we divided the patients into 2 groups according to 28d instead of 90d survival status for 2 reasons. One is that some patients were lost to follow up after 28d; and secondly, twenty-eight survival status was more wildly used to evaluate the prognosis of critical ill patients. Therefore, we only reported the 28 day mortality in the results.

*The role of sepsis should be clarified. More than 40% of the study population suffered from sepsis, however, septic AKI obviously did not play a role. Although this entity is difficult to diagnose, at least a comment might be helpful.*

We totally agree with the reviewer’s comments. Sepsis is fairly difficult to diagnose, and more importantly, our population was not confined to the ICU or critical ill population. Both contributed to the discrepancy between our study and the previous studies. According to the reviewer’s advice, we have added some words in the discussion section.

In addition, 43.8% of the AKI patients suffered from sepsis in our study. However, septic AKI obviously did not play a role in AKI prognosis. This is different from
many previous studies. The PICARD study showed that sepsis in AKI patients portended a poor prognosis, with higher mortality rates and relatively longer length of stay. Different study population may contribute to the discrepancy that our patients were not confined to the ICU or critical ill patients.
Response to Professor Kamyar Kalantar-Zadeh:

Whereas the concept of CRP to prealbumin (or albumin or cholesterol) ratio is interesting, the authors need to add 1-2 sentences based on what (data?) they were (inspired) to advance this metric? Are they data showing that the inverse of prealbumin (1/prealbumin) is a better death predictor than prealbumin itself?

In the previous studies, inflammation and malnutrition were both associated with the prognosis in critical patients including AKI patients. The correlation between inflammation and malnutrition was close and complex because inflammation could lead to malnutrition, as well as malnutrition was an adverse factor for the control of inflammation. In Pinilla’s study the ratio of CRP to prealbumin (CRP/prealbumin) was associated with the severity of organ dysfunction in critically ill patients. So the ratio of CRP and nutritional markers including albumin, prealbumin and cholesterol were studied. We have had some modification in the revised manuscript. In our data, the inverse of prealbumin (1/prealbumin) is the same as prealbumin itself.

In addition, the correlation between inflammation and malnutrition was close and complex because inflammation could lead to malnutrition, as well as malnutrition was an adverse factor for the control of inflammation. Pinilla et al reported that the ratio of CRP to prealbumin (CRP/prealbumin) was associated with the severity of organ dysfunction in critically ill patients. However, no study reported that the combination of the inflammatory and nutritional markers could predict the mortality of AKI patients.

A simple Figure (such as 4) that compares the quartiles of prealbumin, CRP and CRP to prealbumin would be useful.

We totally agree with the reviewer’s suggestion, and add figures illustrating the hazard ratio for prealbumin and CRP changes according to quartiles in the revised manuscript.

In Figures 2 and 3 and in the Abstract the number of patients in control groups need to be mentioned, e.g.: “In addition, CRP and prealbumin were also measured in healthy controls (n=xx) , maintenance hemodialysis (n=xx) and peritoneal dialysis patients (n=xx) and then compared with AKI patients.”

Thanks for the comments. We have added them in Abstract and in Figures 2 and 3.

In addition, CRP and prealbumin were also measured in healthy controls (n=45), maintenance hemodialysis (n=70) and peritoneal dialysis patients (n=50) and then compared with AKI patients.

Recent data on prealbumin and outcomes in kidney disease deserve mentioning here. The paper by Rambod et al in AJCN 2008 or 2009 (?) shows that lowering
prealbumin was an even more sensitive death predictor than albumin. The trial by Cano et al in JASN (2006 or 2007?) showed that prealbumin drop over time was associated with increased mortality.

Thanks for the advice. We have added the results of the studies in the Background.

The study by Cano et al showed that an improvement in prealbumin during nutritional therapy was associated with a decrease in morbidity and mortality in malnourished hemodialysis patients. Another study also reported that even though baseline serum prealbumin may not be superior to albumin in predicting mortality in maintenance hemodialysis (MHD) patients, prealbumin concentrations < 20mg/dL were associated with death risk in those patients and a fall in serum prealbumin over 6 month was independently associated with increased death risk.

In the Results section of the Abstract the p-value is not clear to represent p-for-trend or ANOVA or some other test statistics? “The hazard ratio was 1.00 (reference), 1.85, 2.25 and 3.89 for CRP/prealbumin increasing according to quartiles (p=0.01).”

We regret for our carelessness. The $p$ value represents p-for-the trend. We have added it in the revised manuscript.

The hazard ratio was 1.00 (reference), 1.85, 2.25 and 3.89 for CRP/prealbumin increasing according to quartiles ($p=0.01$ for the trend).

SOFA needs to be spelled out in the Abstract. Its use may not be necessary. Same goes with RIFLE, although RIFLE is a more known acronym in nephrology practice.

They have been corrected in the revised manuscript.