Author’s response to reviews

Title: Association of plasma macrophage colony-stimulating factor with cardiovascular morbidity and all-cause mortality in chronic hemodialysis patients

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Author’s response to reviews:
Dear editor and reviewers,

Thank you very much for your careful review and constructive suggestions to our manuscript “Association of plasma macrophage colony-stimulating factor with cardiovascular morbidity and all-cause mortality in chronic hemodialysis patients”. Your comments are valuable and helpful for us to improve our paper. We are very grateful. We have tried our best to revise and improve the manuscript, and given an explanation according to each issue. The revised portion is marked in red in the revised manuscript. We also responded point by point to the comments as listed below. Thank you for your consideration again.

Yours sincerely,

Rui Zeng

Responds to Reviewer #1:

1. In terms of statistical analyses, the associations of M-CSF elevation with either cardiovascular morbidity or all-cause mortality should be tested in the same methods, in combination of Kaplan-Meier analysis and ensuing uni- or multi-variate Cox regression analysis. This is much easier for readers to well understand the clinical significance of M-CSF elevation. The reviewer wonders why the different method was employed in analysis for cardiovascular morbidity, i.e., logistic regression only.

Thank you a lot for your advice. Since four patients were treated in other hospitals after cardiovascular events during the follow-up period, the patients themselves only remembered the specific year and month of the event, not the specific date. In these days we have reviewed their medical records and re-analyzed their cardiovascular events. Then, we performed Cox regression analysis instead of logistic regression analysis to identify the risk factors for cardiovascular events in dialysis patients. We have removed the Table 3 and added as the new Table 3.

Thank you very much for your constructive suggestions. We have carefully read the three documents, and the comments in these articles showed M-CSF induced both scavenger receptor and CD 36 expressions accelerated atherosclerosis, which explained the mechanism why there are more adverse events in dialysis patients with high M-CSF levels. Therefore, we cited these documents in the discussion and made a streamlined summary in page 10 in line 2-4.

3. The longitudinal study of plasma M-CSF level in the dialysis survivors showed that plasma M-CSF levels increased with HD years; whereas ΔM-CSF-low group had longer hemodialysis duration than ΔM-CSF-high group, as shown in Table 2. How do the authors explain this clinical inconsistency?

Thanks for your question. In Table 2, the patients were divided into M-CSF-low and M-CSF-high groups according to the median difference between the end of follow-up and the beginning of follow-up. In the ΔM-CSF-low group, the M-CSF level at the end of follow-up should be higher than at the beginning of dialysis. In addition, although there were small differences in hemodialysis duration between the two groups, there was no statistically significant difference.

4. There are some typographic errors in data described in the text.

Thanks for your suggestion. We sincerely apologize for the typographic errors. We have tried our best to correct the errors in the revised version of the manuscript.

Responds to Reviewer #2:

1. Given the effect of timing of blood sampling on the measurements, mid-week dialysis session may be optimal compared to other dialysis sessions.

Thanks for your valuable suggestion. We are sorry to ignore the fact that the mid-week dialysis session may be the best blood collection time. However, in order to avoid the impact of blood sampling time on the measurement, all the samples were collected in the same dialysis session and then tested at the same time by ELISA or CBA.

2. In Abstract and Methods section, the author indicated that 52 hemodialysis patients were recruited, while in Results—Baseline characteristics of study population, "Among the 54 patients with HD, 29 were male and 24 were female, …", which 54 hemodialysis participated the study. But I noticed that "29 + 24" should be 53. So how many patients were recruited?
Thanks for your question. We express our sincere apologies for such mistakes we made. In fact, as mentioned in most of the text, we recruited 52 hemodialysis patients in this study, 29 of whom were male and 23 were female. We have corrected these errors in the revised manuscript in page 7 in line 1.

3. In Table 3 multivariate logistic regression model, age and systolic blood pressure were adjusted. In my opinion, the confounding risk factors for cardiovascular events, such as sex, age, hemoglobin, comorbidities and so on, should be adjusted too. And given the prospective cohort study, Cox proportional hazard model should be used to identify the risk factors for cardiovascular events in this population.

Thank you for your valuable advice and guidance. Following your suggestion, we used cox regression analysis instead of logistic regression analysis to identify risk factors for cardiovascular events in these hemodialysis patients. In the multi-factor cox regression model we added some confounding risk factors other than age and systolic blood pressure.

4. To find the risk factors for all-cause mortality, the authors used Cox regression model, but the number of death was only 8. The authors found a cut-off value of M-CSF using ROC, then categorized patients into two groups according to the cut-off value. Please showed the number of patients at risk in two groups.

Thanks for your question. As mentioned in the manuscript, our study had some limitations. One of them is the limited number of samples, so the number of death is only 8. Five patients died in the high M-CSF level group and three patients died in the low M-CSF level group. This result has been added to the revised manuscript in page 8 in line 14-15.