Author’s response to reviews

Title: Malnutrition-inflammation is a risk factor for cerebral small vessel diseases and cognitive decline in peritoneal dialysis patients.

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The authors’ response letter has been included as a supplementary file

Dear editors and reviewers:
Thank you very much for your review of our manuscript “Malnutrition-inflammation is a risk factor for cerebral small vessel diseases and cognitive decline in peritoneal dialysis patients”.

We have considered all of the reviewers’ comments and revised our manuscript, showing the changes in blue text. A point-by-point response to each suggestion and concern is provided below:

Reviewer 1 (Che-Yi Chou):

The authors accessed the association of malnutrition-inflammation and cerebral small vessel diseases (CSVD)/cognitive impairment in 72 chronic peritoneal dialysis (PD) patients of one hospital. The CSVD was determined using brain MRI images and the cognitive function was evaluated using the Chinese version of the MMSE and MoCA. They found that nPCR was an independent risk factor for lacunar infarcts and impaired cognitive function. The presence of lacunar infarct was an independent risk factor for cognitive function decline. I have some suggestion about the study design.

1. The dependent factors were CSVD, cognitive impairment and the independent factors were nPCR and CRP based on the title. The CSVD was determined using MRI and the cognitive impairment was determined using MMSE and MoCA. Ideally, the analysis should have the association between nPCR and CSVD/cognitive impairment, CRP and CSVD/cognitive impairment, followed by the interaction between nPCR and CRP would be critical in the analysis. However, I can not see this through Table 2-4.

We really thank the reviewer for her/his comments and suggestions. This is an excellent suggestion.

The association between nPCR and 4 different signs (features) of CSVD was demonstrated in Table 2, the association between CRP and CSVD was also showed in Table 2.

Meanwhile, the association between nPCR and cognitive function was analyzed in Table 3, so did the association between CRP and cognitive function. We use MMSE/MoCA scores (which was a continuous variable) to reflect cognitive function in these analysis instead of cognitive impairment. The reason of that was: according to the score of MMSE/MoCA, 25% and 86.8% of our patients could be diagnosed as cognitive impairment, correspondingly. While our sample size was 72, if we use cognitive impairment which is a dichotomous variable, the multivariable analysis model will be unstable, which would result the abnormal standard errors of some
We agreed with the reviewer’s suggestion about the interaction between nPCR and CRP. As indicated by the term "malnutrition-inflammation-complex syndrome, MICS", it is thought that nPCR and CRP might be related. Actually, in model 4 of Table 2 and 3, in the multivariable logistic regression model, we had adjusted for nPCR and hsCRP (according to whether nPCR/hsCRP is a significant variable in univariate analysis), we had added the explanation of the adjusted covariates of model 4 in Table 2 (Results section, separate file) and Table 3 (Results section, line 312-313, page 14). Additionally, we analyzed the interaction between nPCR and CRP in the charts below (please see these in the attached files). Maybe it is because of the limitation of our sample size, we did not find a significant interaction between them. Thus, we added this point as our limitations of our study (Discussion section, line 438-439, page 22).

2. Table 4 showed the association between CSVD and cognitive function. The results may not be surprised because they are both dependent factors. The brain MRI findings lacunar infarcts and WMHs are correlated to cognitive impairment.

We thank the reviewer for pointing out this.

In previous studies about CSVD in CKD-ESRD patients, few studies focused on comparing 4 CSVD features, thus their conclusion about the feature of SVD that would impact on cognitive function may be inaccurate.

In table 4, we wanted to identify that in the 4 different CSVD features (lacunar infarcts, WMHs, microbleed and chronic intracerebral hemorrhage), which feature is the real lesion that relative to cognitive impairment. In univariate analyses, we found lacunar infarcts and WMHs are correlated to cognitive impairment. Furthermore, in multiple analyses, we found only lacunar infarcts was the independent risk factor of cognitive function. This means the lacunar infarct may be the real lesion which induced cognitive impairment in our PD patient.

3. The prevalence of cognitive impairment "25% and 86.8%" are very different according to the results of MMSE and MoCA tests. As the aim of the study is to determine the association of malnutrition-inflammation and cerebral small vessel diseases (CSVD)/cognitive impairment. Patients with both CSVD and cognitive impairment should be considered as event cases and the analysis can be performed accordingly.

We thank the reviewer for pointing out this important distinction between MMSE and MoCA.
MoCA is more sensitive than the commonly used MMSE in detecting mild cognitive impairment (MCI) (J Am Geriatr Soc. 2005 Apr;53(4):695-9; Neurology. 2009 Nov 24;73(21):1738-45). As most of our patients were MCI, these could partly explain the difference between cognitive impairment ratio of MMSE and MoCA.

We agreed with the reviewer’s suggestion to use patients with cognitive impairment as event cases. The reason we did not choose to use having cognitive impairment or not (dichotomous) to perform the analysis was because our sample size was not big enough, the dichotomous would result in too little patients in MMSE abnormal group and MoCA normal group. In Table 3, we had done the analysis about cognitive function and nPCR/hsCRP. We use both score of MMSE and MoCA scores as dependent factors, separately. We think this may also reflect the relationship between malnutrition-inflammation and cognitive impairment. We added this limitation in our discussion (Discussion section, line 436-438, page 21-22)

4. The authors may also consider to use the findings of MMSE as the major outcome measurement and MRI findings as the lab findings (independent variable) in the analysis.

We thank the reviewer to point out this.

In table 4, we had already do the analysis suggested by the review. We demonstrated findings of MMSE and MoCA as the major outcome measurement separately in different columns, and MRI findings as independent variable. Although the prevalence of cognitive impairment are very different according to the results of MMSE and MoCA tests, using MMSE score as the major outcome measurement, we got a similar conclusion of using MoCA score as the major outcome measurement that lacunar infarct is an independent risk factor of cognitive function (MMSE or MoCA score) in 4 different signs of CSVD.

Reviewer 2 (Luca Di Lullo):

I have read with interest your paper and I think that it is an impactable one, although I think it needs some minor corrections:

1. Please, provide some data on carotid doppler if you have

We really thank the reviewer for this brilliant suggestion.

We collected carotid Doppler results of our patients performed after our study and would like to add these into our manuscript as the following (Results section, line 214-218, page 11) ” 18.1% patients reported themselves had been diagnosed with atherosclerosis of carotid, coronary, or
extremities arteries. In these patients, 5 of them had carotid atherosclerosis. During a year after our study, 27 more patient received a carotid doppler and 22 of them were identified with carotid atherosclerosis, but only 2 of them were diagnosed with carotid stenosis.”

Although there was a time lag between our study and the ultrasound, the Doppler results still could reflect a severe carotid atherosclerosis burden in our PD patient

2. It could be helpful to compare your data with control population with same characteristics

We respect the reviewer’s suggestion and agree that control population with similar characteristics would make the conclusion more convincing. However, it is difficult to find a cohort of health control with similar demographic who had a nutritional evaluation and CSVD/cognitive function assessment.

But, we believe that the following attributes of our study highlight its uniqueness:

Our study is the first study to highlight the association between nutrition-inflammation status and cerebral SVD/ cognitive function in PD patients. It is known that malnutrition-inflammation are related to atherosclerosis (known as MIA), so we deduce that the CSVD may also related to nutrition and inflammation. Malnutrition and microinflammation are generally common in PD patients, but unusual in general population. Thus PD population became a good study population of those hypotheses.

In our study, we found cognitive impairment in our PD population. In the discussion section, we compared the average MMSE and MoCA score of our patient to a reported average MMSE and MoCA score from a community population of similar age (50-59) and region (Beijing urban residents), 27.6±3.1 and 21.7±5.6 vs. 29.79±0.46 and 27.69±1.57, respectively. Those results also corroborate our conclusion of the declined cognitive function in PD patients.

Overall, while we agree with some of the points of the reviewer, we believe our study advances the field, especially among those living in China. A controlled study would become our next step as an extension of present study in the future.

Editors:

We had made the revised manuscript conforms to the journal style. We also corrects some typos (including fig 1).