Author’s response to reviews

Title: Clinical characteristics and outcomes in microscopic polyangiitis patients with renal involvement: a study of 124 Chinese patients

Authors:

Jia Shi (463659484@qq.com)
Qing Shen (sq4817@163.com)
Xue-Mei Chen (1557451771@qq.com)
Xiao-Gang Du (cqmudxg@163.com;1248641770@qq.com)

Version: 1 Date: 24 May 2019

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Clinical characteristics and outcomes in microscopic polyangiitis patients with renal involvement: a study of 124 Chinese patients” (ID: BNEP-D-19-00112). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the response to the reviewer’s comments are as follows:

Reviewer 1

1. It might be helpful if the authors could explicate a little on why identifying the predictors of these specific outcomes are essential. Knowledge for knowledge sake is important, but helping the reader understand why it is important or relevant to them in the introduction may help us better appreciate why the authors sought to embark on this project.

Response: Thanks for your valuable advice. We have revised our backgrounds and explicated why we analyzed the predictors of death and ESRD in MPA patients with renal involvement, the revised detail could be found in backgrounds, paragraph 3
2. While we might be able to appreciate that this is an exploratory study, did the authors have any a priori hypotheses based on the work done in other European MPO samples? It would also help us appreciate, in the introduction or methods, why certain lab markers were included/not included (e.g., what was imaging necessary for, why was 65 used as a cut-off for age or how and why were the dichotomous cutoffs used, what exactly is general manifestation and how was it statistically used as a composite score/variable or any individual item, what parameters were used for the survival analyses--and why).

Response: As GPA and PR3-ANCA positive is more common in European countries, there are few European studies focused mainly on the outcome of MPA or MPO-ANCA positive patients. Previous study has shown that 39.1% AAV patients had ILD, and AAV patients with ILD have worse prognosis, so we added this in the data collection (Discussion, paragraph 3). Previous studies have shown that age is associated with mortality in AAV patients [6,13,28], and the mean age of our patients was 63.9 years, so we chose 65 years-old as a cut-off for age. In previous study [9], an age of 65 years was also used as a cut-off point. Birmingham Vasculitis Activity Score (BVAS) is an index of disease activity, which might be associated with the prognosis. As the mean BVAS was 15.9 in our study, we chose 15 as a cut-off point. The mean hemoglobin and serum albumin of our patients were 88.6 g/L and 30.1 g/L, so we used 90g/L and 30 g/L as the cut-off point of hemoglobin and serum albumin, respectively. General manifestation includes Myalgia, Arthritis, Fever≥38°C, Weight loss≥2kg. We used gender, age, organ involvement according to BVAS, Serum albumin, ESR, CRP and comorbidities for survival analysis (table 2 and table 3), because previous studies have found that age, renal function, ESR, CRP, ILD, alveolar hemorrhage and comorbidities were associated with prognosis [6,13,15-16,28,31,34,37], so we used these parameters for survival analysis.

3. On a related note, were any power calculations done? If they were not, this should be justified in the methods. The authors might want to consider adding in information regarding informed consent and how data were collected (I understand that some of it is present at the end of the manuscript but having it in text if possible would be helpful).

Response: Thanks for the reviewer’s advice, in this revised paper, we have conducted power calculation using R packag ‘powerSurvEpi’(PMID:6354290, PMID: 15490425) (Methods, Statistical analysis), which found that the power of age, ILD and serum creatinine for death was 0.79, and the power of serum creatinine, ILD and immunosuppressive treatment for ESRD and doubling of serum creatinine was 0.88, the figures are presented below. We did not obtain written informed consent from all participants, because this was a retrospective observational study.
4. Were there any individualised changes made to the patients' treatment regimen (if they were on meds)? It would be helpful if the authors could add in a statement even if no changes were made.

Response: Thanks for the reviewer’s advice. In our study, 31 patients did not receive immunosuppressive treatment for personal reasons.

5. It is unclear if the patients themselves had other comorbid illnesses that may have influenced the results/survival. The manuscript might also benefit from the authors in-text clarification of the definitions of their terms (all cause mortality, renal survival, etc.).

Response: Thanks for the reviewer’s kind advice, we added other comorbid illnesses including coronary heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease or diabetes (Methods, definition and table 1, row 23-30), and we also evaluated these parameters associated with hazard ratio of mortality and progression to ESRD using Cox regression analysis (table 2, row 19-24 and talbe 3, row 19-24), while they are not indepedent risk factors of ESRD or death. We have supplemented the definition of all cause mortality, doubling of creatinine and ESRD in Methods.

6. It may be helpful if the authors highlighted why the ROC analyses were conducted, and what the question was they were trying to answer. Again, having clearer objectives/aims/hypotheses in the introduction would mitigate the confusion in the methods and results sections.

Response: The receiver operating characteristic curve (ROC) analysis was performed in order to provide a description of the variables’ prediction performance. A previous study showed that a peak serum creatinine level over 4.5 mg/dl at the time of diagnosis was a predictive factor for ESRF or death in AAV patient[33], and another study found that the serum creatinine cutoff level for developing ESRD and requiring dialysis therapy was 4.6 mg/dl in MPA patients with renal involvement[17]. So we conducted ROC to determine the serum creatinine cutoff level for poor prognosis and renal survival, all of these has been added in statistical analysis and discussion. Thanks for your kind reminding.

7. The authors may wish to explicate on the limitations and highlight how their findings should be interpreted in view of these limitations, especially given that the cause of death was unclear (much of the assumption of this manuscript is predicated on MPA patients' survival and thus many MPA-related clinical values are used).
Response: Thanks for the reviewer’s suggestion. As most of our patients passed away outside hospital for undetermined reasons, the cause of death could not be analyzed. In future research, more samples should be included, then, cause-of-death analysis could be performed.

8. It would be helpful if the authors could highlight specifically the applicability and clinical implications of their manuscript.

Response: Thanks for the reviewer’s suggestion, we revised the introduction of the manuscript to highlight the applicability and clinical implications.

Minor Suggestions

9. The second paragraph (page 3) reads somewhat confusingly; perhaps the authors might want to consider rephrasing this paragraph to highlight the differences specific to China (I am assuming this is the case so the authors can make a case for their study) and then highlight that even within Caucasian/European populations the epidemiology differs, further underscoring the importance of doing country/region/location-specific investigations.

Response: Thanks for the reviewer’s suggestion, we revised our manuscript in the background, paragraph 2.

10. The sentences in paragraph 3 (pages 3-4) "Many studies have showed... Similar data were also reported..." could be better phrased, especially given that patients with MPA are those who are already a subset of AAV (page 3, paragraph 1, lines 5-6).

Response: Thanks for the reviewer’s suggestion, "Many studies have showed... Similar data were also reported..." has been changed to “Many studies have showed ..., including patients with MPA”(Background, paragraph 3)

11. Not sure whether the journal would take issue with this, but generally in formal writing we refrain from beginning sentences with "And the receiver..." (page 6, paragraph 1, line 4). I would suggest the authors have another round of editing the manuscript not only for typographical errors but also grammatical errors to improve on the clarity of the manuscript.

Response: Thanks for the reviewer’s suggestion, "And the receiver..." has been changed (Methods, Statistical analysis).
12. This is my personal preference--the authors might want to consider using euphemisms for "died" (page 6, paragraph 3).

Response: Thanks for the reviewer’s suggestion, we changed the word “died” in our manuscript. (page 7, paragraph 3)

Reviewer 2:

Major comments:

1. From the inclusion criteria, it suggests that not all patients had a kidney biopsy? The investigators should described in the results how many of the patients had a kidney biopsy? Kidney biopsy findings are not only important for diagnosis, but may also have affected the outcomes particularly ESRD. Those who had chronic findings e.g. interstitial fibrosis and tubular atrophy vs those who had active crescentic diseases surely had different renal prognosis and how did the investigators address this? Also, there are no available data on the kidney biopsy scoring.

Response: Thank you for your suggestion. As most of our patients refused to have kidney biopsy for personal reasons, only 25 patients received kidney biopsy, we could not analyze the pathological characteristics of renal lesions. In future research, more samples should be included, then, pathological features of renal lesions could be analyzed.

2. How did the investigators identify death? Any public database that investigators use? How did the investigators aware that the patients passed away.

Response: We did not use public database. We followed up all of our patients every 3 months by phone call, then, we could learn about patients’ condition. Thank you for your question.

3. How was ILD identified?

Response: Interstitial lung disease (ILD) was defined by the following inclusion criteria: 1) Radiological evidence of ILD on HRCT(such as reticular abnormality or honeycombing with or without traction bronchiectasis), and/or lung function testing consistent with ILD. 2) The exclusion of another possible aetiological factor(such as drugs and dust) in the development of ILD. All of these has been added in the manuscript (page 5, paragraph 2). Thank you for your kind reminding.
4. The lack of cause of death might be limitation to understand

Response: Thanks for the reviewer’s suggestion. As most of our patients passed away outside hospital for undetermined reasons, the cause of death could not be analyzed. In future research, more samples should be included, then, cause-of-death analysis could be performed.

5. How did the investigators deal with the patients who had ANCA testing by IF (cANCA and pANCA), but did not have ELISA testing? Need to be clarified.

Response: In our study, ANCA was measured by both IF and ELISA. Thank you for your question.

6. Strongly suggest that Doubling of serum creatinine should also be one of clinical outcomes of interest.

Response: Thanks for the reviewer’s valuable suggestion. The composite of ESRD and doubling of serum creatinine was used as endpoint of renal death, and 5 more patients reached the renal outcome (page 5, paragraph 2). The multiple Cox regression analysis suggested that serum creatinine ≥500 umol/L at diagnosis, ILD and immunosuppressive treatment were associated with renal prognosis, which is in accordance with our previous study. (table 3)

7. The investigator did not describe how many patients received Rituximab treatment.

Response: No patient in our study received Rituximab treatment, and we added it in the manuscript (page6, paragraph 1). Thanks for your kind suggestion.

8. When the investigators mentioned baseline creatinine, how did the investigators identify baseline creatinine? The investigators should describe more how to define baseline creatinine. Most recent vs. minimum? These will affect the sensitivity and specificity of AKI diagnosis, Please see The use of the most recent creatinine vs. the minimum value of SCr measurement as baseline creatinine (PMID: 26032233)

Response: Thanks for the reviewer’s suggestion. As previous studies, all of our values were collected at the time of diagnosis, (PMID: 28231769, PMID: 24183110 ,PMID: 26980047, PMID: 23223225 et, al). “Baseline characteristics” used here is not appropriate. We have changed it to “Patients characteristics at diagnosis”. Sorry for our mistake.
9. How did the investigators deal with patients without baseline creatinine is also unclear. Did the investigator use? SCrGFR-75, when baseline outpatient SCr was not available (PMID: 26748909)

Response: Thanks for the reviewer’s suggestion. All of our patients were hospitalized patients. All of our values were collected at the time of diagnosis. We’ve changed “Baseline characteristics” to “Patients characteristics at diagnosis”.

Additional comments:

Some revision of the English language is needed. There are some parts of the paper where it is quite difficult to make sense of some sentences. English edit will help to improve the quality of the manuscript.

Response: Thanks for the reviewer’s advice, we revised the sentences.

"kidney biopsy show pauci-immune necrotizing glomerulonephritis" is not correct in grammar.

Response: "kidney biopsy show pauci-immune necrotizing glomerulonephritis" has been changed to “presence of pauci-immune necrotizing glomerulonephritis in a renal biopsy”

"Age have previously been shown to predict mortality in AAV" is not correct in grammar.

Response:"Age have previously been shown to predict mortality in AAV" has been changed to “Previously studies have shown that age is associated with mortality in AAV patients”.

"mainly because a greater rate of severe renal failure at disease onset" is not correct in grammar.

Response:"mainly because a greater rate of severe renal failure at disease onset“ has been changed to “mainly because MPA patients has developed severe renal failure at the onset of the disease”

"which is accordance with the result of previous study" is not correct in grammar.

Response:"which is accordance with the result of previous study" has been changed to "which is in accordance with the result of previous study"
It is not professional in academic writing to use "And" at the beginning of sentences.

Response: "And the receiver..." has been changed to “Receiver-operating characteristic curves”

The sentence "All patients were followed-up till death" should be modified. It is not perfectly professional in academic writing.

Response: "All patients were followed-up till death" has been changed to “All survivors were followed up until July 2018”

"in UK" should be "in the United Kingdom"

Response: "in UK" has been change to "in the United Kingdom"

Abstract: Background "Microscopic polyangiitis (MPA) is a chronic multiple-system disease, renal involvement is common in MPA and is associated with the outcome." is not well written and should be modified.

Response:"Microscopic polyangiitis (MPA) is a chronic multiple-system disease, renal involvement is common in MPA and is associated with the outcome." has been changed to “Microscopic polyangiitis (MPA) is a systemic autoimmune disease, renal involvement is common in patients with MPA and is associated with prognosis”.

We would like to express our great appreciation to you and reviewers for comments on our paper. We try our best to improve the manuscript and hope that the correction will meet with approval. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Xiao-gang Du