Author’s response to reviews

Title: Oral candidiasis is a significant predictor of subsequent severe infections during immunosuppressive therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis

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Version: 1 Date: 03 Jul 2019

Author’s response to reviews:

Thank you for reviewing our paper

Thank you for reviewing our paper and for the valuable suggestions. We have revised our paper accordingly.

1) Restrict the conclusion (abstract and elsewhere) to this particular hospital. Replace the term "independent" with "adjusted for ..." and add the specific covariates tested.

We replaced “independent predictor” with “one of the predictors” in the Conclusions of the Abstract and Conclusions of the main manuscript as follows:

“OC is one of the predictors of subsequent severe infections.”

We added the following sentence in the last paragraph of the Discussion as a study limitation:

“Second, this study has a single-center small cohort design and the observation period was short; therefore, our results should be validated in other multicenter large cohorts with longer follow-ups.”
If it is insufficient, please advise to modify our expressions as your comments.

2) Clarify whether OC exposure was established as any OC during follow-up. If so, modify analysis to estimate HR before and after first OC, since some patients may contribute to both groups (that is, the analysis may require person-time as unit).

In the OC group, each patient had one episode of OC, and none had relapsed. As described in our manuscript, in the OC group, all severe infections occurred after the first OC episode at a median of 2.5 months (interquartile range: 0.3–15 months). Therefore, we estimate the HR of severe infection only after the first OC.

3) Clarify if OC treatment was systemic. If so, you may need to discuss the possible interference with the outcome.

Regarding OC treatment, although all patients were prescribed oral antifungal drugs such as itraconazole or fluconazole for systemic effects, we consider that OC treatment itself does not directly influence the outcome of severe infection.

We added the following sentence in the fourth paragraph of the Discussion:

“Regarding OC treatment, although all patients were prescribed oral antifungal drugs such as itraconazole or fluconazole for systemic effects, we consider that OC treatment itself does not directly influence the outcome of severe infection.”

4) Clarify which models were tested. You mention three, but only one seems to be presented in the tables. Also, it is not clear if the interaction term mentioned was the only one tested. A way to clarify all this could be to extend Table 2 with the models and terms tested, as well as adding more information in a table footnote (such as R2 or similar). If it is the case, describe in Methods the model selection strategy.

In line with the reviewer’s suggestion, we added the following sentence as footnotes to Tables 1 and 3: “For continuous variables, the Wilcoxon rank-sum test was performed to assess the significance of inter-group differences. Categorical variables were expressed as percentages and compared by using Fisher's exact test.”

Furthermore, we inserted the following sentence in the second paragraph of the Statistical analysis section.
“To assess whether an association between methylprednisolone therapy and outcome was different in the OC and non-OC groups, the effect modification between methylprednisolone pulse therapy and the OC group was assessed by the inclusion of interaction terms in the multivariate Cox proportional hazards models.”

5) Amplify the sample size limitation: The CIs are wide, therefore the effects you find maybe very small (or very large). I strongly suggest that you make available as an open supplement the anonimized dataset, the computer code for analysis and the diagnostic output.

The sample size of this study was indeed small; therefore, we added the following sentence in the Discussion as a study limitation: “Second, this study has a single-center small cohort design and the observation period was short; therefore, our results should be validated in other multicenter large cohorts with longer follow-ups.”

As suggested, we made our data set available as a supplement.