Author's response to reviews

Title: The epidemiology, antifungal use and risk factors of death in elderly patients with candidemia: a multicentre retrospective study

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Author's response to reviews: see over
Dear Dr. Ramos,

Thank you so much for offering us this opportunity to revise this manuscript, entitled "The epidemiology, antifungal use and risk factors of death in elderly patients with candidemia: a multicentre retrospective study".

We would also like to show our heartily appreciation for all the reviewers. Their comments are very valuable and helpful in improving the quality of our manuscript. As detailed in the Response to Reviewers and highlighted in the revised manuscript, we have tried our best to address all the comments. In addition, according to the comments from the reviewers, we adjusted the age range of the younger group and included several additional indicators in the analysis of risk factors for death. Accordingly, the statistics related with the above issues were redone by a statistics expert for this revised paper. We also placed the Competing Interests section, Authors Contributions section and Acknowledgements section after the conclusions. Furthermore, a native English-speaking editor helped us improve the English language text of the manuscript. Please let us know if further language editing is needed. We are very pleased to use the language service recommended by you.

We hope to hear from you soon on this manuscript.

Thank you again for your time and effort.

Sincerely yours,

Hao Wang, MD            Dawei Wu, MD
We would like to thank all reviewers for their critical evaluation of this manuscript. In this letter, we have responded point-by-point to all the comments (shown in blue) and all the changes were highlighted in the revised manuscript.

**Responses to reviewer's report:**

**Reviewer: Roberto Luzzati**

**MAJOR COMPULSORY REVISIONS**

The aim of this retrospective study is quite interesting. It’s well defined in the text but not in the abstract of the manuscript (please, see BACKGROUND).

Response: Thanks for your suggestion. The aim of the study was to determine the peculiarities in the epidemiology, antifungal management and clinical risk factors of death in the elderly population with candidemia. We have revised the abstract in P2, L3 to provide a clear description of the aim.

The methods of the present study should include some more information.


Response: Your comments are really valuable and helpful. Sepsis is the best definition to illustrate the clinical condition of patients at the onset of candidemia. As suggested, we have cited the reference in the methods section of the manuscript (P5, L17).

2. The definition of severe hypoalbuminemia is lacking in the methods.

Response: Severe hypoalbuminemia was defined in the literature as serum albumin levels < 23g/L [1]. We have added the definition of severe hypoalbuminemia in the methods section of the manuscript (P7, L9).

3. Concurrent infections: do you mean bloodstream infections ? please, this should be specify.
Response: This is very helpful comment. Actually we mean the concurrent bloodstream infection, as mentioned in the Table 3. We have re-written this part and specified the definition of concurrent bloodstream infection in P7, L17 according to the suggestion.

4. Data on antifungal administration < 2 weeks before the microbiological documentation of candidemia are accurately reported in table 2. However, regarding the outcome of candidemia the potential role of empirical antifungal therapy could be different from that of antifungal prophylactic therapy. As a consequence, the analysis of risk factors for death (table 4) must include separate data regarding antifungal agents given as empirical treatment and prophylaxis. To my opinion, this is crucial in order to understand the role of such different antifungal regimens in the outcome of candidemia episodes. This issue should be discussed in the discussion section of the manuscript.

Response: True, the potential role of empirical antifungal therapy could differ from that of antifungal prophylactic therapy in terms of outcome of candidemia. We were also interested in the role of such different antifungal regimens in the outcome of candidemia episodes. Accordingly, we added separate data in the analysis of risk factors for death, as shown in Table 4. The use of empirical treatment and prophylaxis treatment was increased in the survivors, but probably because of the small case numbers, these data did not differ between survivors and non-survivors. Therefore, empirical or prophylaxis treatment was not included in the multivariate regression model. However, when combining those prior antifungal regimens, we found a significant difference between the two groups, defined as “antifungal therapy administered before microbiological documentation” and thus could improve the outcome for elderly patients. The above issues were discussed in the discussion section (P14, L9~ P14, 19) in this manuscript.

We realized that the case numbers in current study is limited due to shorage of time and enrollment of patients. We are currently carrying out another prospective project on candidemia in Qilu hospital of Shandong University (2014 July to present). We expect to enroll more centers and cases in the next several years. Hence in the
future project, we will be having a better chance to figure out the role of different antifungal regimens in the outcome of candidemia episodes.

5. The antifungal susceptibility testing is reported in the methods but such results are incompletely shown in the result section (data regarding antifungal resistance of the major Candida non-albicans species are missing). These data should be reported and compared between young and elderly patients in a new table.

Response: The anti-fungal susceptibility testing for fluconazole, voriconazole and caspofungin was reviewed and the resistance rates were recorded with CLSI antifungal drug susceptibility thresholds. The data has been provided and shown in the results section (P8, L16 ~ P9, L8) and a new Table (Table 1), with details about the resistance of major non- albicans Candida species in that Table. Furthermore, the discussion related to resistance of Candida species has been added and the conclusion has been reconsidered accordingly.

6. Among predisposing factors of candidemia, the placement of CVC is reported in table 1 but data regarding CVC-associated candidemia are not available. Removal of CVC is a well-known and very important measure for the management of candidemia. These data should be reported and included in the analysis of risk factors for death. On the contrary, this issue must be added among the limitations of the study.

Response: Thanks for this courtesy reminder. According to the suggestion, we have reported the data for CVC placement and CVC-associated candidemia in the results section and Tables 4 and 5. CVC retention has a negative impact on outcome in patients with candidemia [2, 3]. We compared the rate of CVC removal between survivors and non-survivors in Table 5, and found that the rate of CVC removal was higher for survivors (p < 0.10). Thus removal of CVC was included in the following multiple logistic regression model, but did not play a role as independent protective factor for death. Compared to the results from previous reports [2-4], the removal rate for the elderly patients in this study is relatively low (14/32, 43.8%), so the real percentage of CVC-related candidemia as well as the effect of CVC removal on prognosis might have been underestimated. Thus, awareness of the risk of CVC
retention needs to be strengthened in the management of candidemia in Chinese hospitals. The above issues were added in the limitations of the study.

7. The discussion and conclusions must be reconsidered according to the previous issues. In particular, current results regarding risk factor analysis do not allow to state that ‘the antifungal therapy should be early implemented before microbiological documentation’ in this patient population.

Response: Regarding the previous issues pointed by the reviewer, we have addressed them in the revised the manuscript and in this letter. As for the conclusion, we have revised to better represent the data we presented in this manuscript.

Once again, thank you very much for your constructive comments and suggestions.

References:
Responses to reviewer's report:

Reviewer: Geraldine Hall

Major revisions

1. Was the age of the elderly patient for the study defined before or after the data was collected? It should have been done before. I would like the authors to consider adjusting the "test" and "control" groups that were compared, for example analyze the date for those above 60 or 65 and those between 16 and 50 or 55. Have a larger than 1 year difference between the young and the elderly. What was the exact range of the age groups? Please give the range of ages for each group.

Response: The age of the elderly patients was defined before the data were collected. Having a larger than 1-year difference between the young and older patients would make a more significant difference in the indicators when comparing the two groups. According to your suggestion, we re-defined the range of ages for the younger group and had a 4-year difference between the two groups. Considering the small sample size of this study, we used 4 years because a larger difference would lead to more cases excluded. The exact range of the younger group was 16-60 years and the elderly ≥ 65 years, which was defined in the abstract section (P2, L6) and the methods section (P5, L18) of the revised manuscript. Accordingly, the case number of the younger group was adjusted and all statistical analysis related to younger patients was redone.

2. Was anti-fungal susceptibility testing done? If so, the results should be provided. One of your conclusions is that there was more resistance of the non- C. albicans cases, and this information should be provided.

Response: Thank you for the suggestion. The anti-fungal susceptibility testing for fluconazole, voriconazole and caspofungin was reviewed and the resistance rates were recorded by using CLSI antifungal drug susceptibility thresholds. New data are provided in a new Table (Table 1) and are summarized and discussed in the main text. In brief, the resistance to fluconazole and voriconazole of non-C. albicans species in elderly patients was approximately double that of younger patients [30.6% (11 of 36) vs. 15.1% (8 of 53), 8.3% (3 of 36) vs. 3.8% (2 of 53), respectively]. However, all
isolates in younger and elderly patients were susceptible to caspofungin. The detailed information related to the resistance of non-*C. albicans* cases is provided in Table 1.

Minor essential revisions
1. There are a number of occurrences where an "s" was used instead of "z", for example, hospitalization and colonization and hypothesized and characterize in Background. In Materials and Methods, standardized;

Response: We have made the corrections.

2. In Materials and Methods and In Abstract, 4 tertiary centers were used to collect the data but in the Discussion, the first statement suggests that strength of study is the use of 5 centers. Please clarify.

Response: As mentioned in the Abstract and the Methods section, there are 4 centers in this study: Qilu Hospital of Shandong University, Qianfoshan Hospital affiliated with Shandong University, Jinan Center Hospital affiliated with Shandong University, and Liaocheng People’s Hospital affiliated with Taishan Medical College. We have made the correction in the Discussion section accordingly (P11, L8).

Discretionary Revisions
1. In the discussion, you mention prior exposure as a reason for increased resistance. Was there any attempt to document prior anti-fungal exposures between the young group and the elderly?

Response: We are very interested in this issue, but the data was difficult to be obtained because of the limitation of this retrospective study, which has a main problem of the lack an electronic medical-records system in all hospitals and thus limited our ability to obtain exact prior antifungal exposures. This issue was added as a limitation in the limitations section of the manuscript. However, though not relevant to this manuscript, we are carrying out a prospective project on candidemia in Qilu hospital of Shandong University (2014 July to present). We expect to include more
centers and collect more cases and in the following several years. In this research project, we will try to document prior anti-fungal exposures between the younger group and the elderly according to your suggestion.

2. Please define if any chart review was done to determine whether candidemia was indeed evidence of an infection or transient fungemia? Provide a definition of how this was determined.

Response: In this study, an episode of nosocomial candidemia was defined as one or more blood cultures positive for *Candida spp.* and persistent clinically apparent signs and symptoms of sepsis for more than 48 hours [1]. The definition of candidemia was widely used in other studies [2-4]. As a consequence, the patients with transient fungemia, who mostly presented without clinically apparent signs and symptoms of sepsis or with signs and symptoms of sepsis for less than 48 hours, were thus excluded from this study.

Finally, thanks to you for your time and effort in reviewing our paper.

References:

Responses to reviewer's report:

Reviewer: Bradley Ford

Major comments:

1) The latest CLSI guidelines are being used here. Still, there is uncertainty over what is being defined as "resistant". Page 8, line 22 states 10 of 59 isolates were resistant from young patients. First, per the previous paragraph I count 58 isolates, not 59. Secondly, there is no susceptible category for C. glabrata anymore -- are authors counting the "SDD" category as susceptible, considering that differences in dosage might be needed to cover it? Secondly, which non-albicans yeast were nonsusceptible, and were the C. krusei counted in this group? If it is made clear what isolates were resistant it will be easier to appreciate why the rate of resistance was double in the elderly; this data should be presented and discussed on page 12 (top).

Response: Thank you for your comments. We have reviewed all the reported data again and made sure that all the data are correct and error free. We redid the statistical analysis related to younger patients, because the age range of the younger group was adjusted from 16-64 years to 16-60 years according to the comments from another reviewer. Thus the resistance rate to fluconazole of non-albicans Candida species in younger patients was then 15.1% (8 of 53 isolates).

Regarding the drug susceptibility thresholds for C. glabrata and fluconazole, the following breakpoints were used in this study: SDD, \( \leq 32 \) mcg/ml; R, \( \geq 64 \) mcg/ml [1]. Because of no susceptible category established for C. glabrata, we counted the resistant isolates using the resistance breakpoints. However, when the isolate is identified as C. glabrata and the MIC is \( \leq 32 \) (SDD), the patients should receive a maximum dosage regimen of fluconazole for a better curative effect according to CLSI guidelines.

According to the suggestion, we report the detailed resistance of the major non-C. albicans species in the results section (P8, L16 ~ P9, L8) and a new Table (Table 1). C. krusei was also counted in this group. In the current study, C. tropicalis, C. parapsilosis and C. glabrata were associated with a higher resistance in the elderly patients than younger patients (Table 1), for doubled resistance rate to fluconazole in
the elderly patients. These data are presented in the main text and discussed on P12-13.

2) Summarizing some of the main demographics and findings should be done in the main text.

Response: The main demographics are summarized in the first paragraph of results section (P8). The summarized findings have been also added in different paragraphs of the results section according to your suggestion.

3) Epidemiology, microbiology and statistics associated with Candida species should be placed in the main text.

Response: In accordance to the comments from the reviewers, the anti-fungal susceptibility testing for fluconazole, voriconazole and caspofungin was reviewed and resistance rates were recorded. The detailed resistance to different antifungal agents of Candida species are shown in a new table (Table 1); the main points of the epidemiology, microbiology and statistics associated with Candida species are placed as an independent part in the results section of the main text.

Minor comments:
While overall well-written, some editing for English usage should be done prior to publication. Currently these do not obscure the intended meaning.

Response: Thank you so much for the kind evaluation of our manuscript. The English language has been edited by a native English-speaking editor. Please let us know if further language editing is needed.

Finally, we sincerely thanks for your helpful suggestion again!
Reference: