

Dear Editors:

Really thanks for your effort put on this manuscript, those advices and suggestions are very useful for upgrading our research. For the reason of explorative study, we can give response based on our data and literature to some questions you raised, however, some of those question raised is very hard to provide a satisfactory answer, we just discussed those question as possible as we can.

we carefully revised the manuscript again, including: 1. upload the PDF version of the Copyright License Agreement Form that has been signed by all authors. 2. revise the manuscript duplicated parts according to the CrossCheck report uploaded by the editor. 3. provide the certificate of funding agency. 4. The audio file was uploaded. 5. Revised the reference file format in the manuscript, add PubMed citation numbers (PMID) and DOI citation to the reference list and list all authors. 6. Replace the abbreviations in the table with full names, delete *, # in the manuscript, use superscript letters revised the writing format for P-values.

A point-to point response to reviewers' and Editor's comment as following.

Reviewer No.54787

Reviewer #1: This is an interesting manuscript facing with the relevant problem of factors influencing antibiotic associated diarrhea in intensive care unit. The manuscript is well written and the conclusions are supported by the statistical analysis both uni and multivariate. The limitations of the study is the relative small number of patients, the retrospective study is acknowledged by the authors themselves. Overall the study is useful for physicians dealing with such problems

Response: Thank you for your opinions. Thanks editors and Reviewer, we hope our manuscript will be published soon.

Reviewer #2: Comments for authors: I am most grateful for this review opportunity. The article is a well-structured, single-center, case-control study discussing risk factors for antibiotic-associated diarrhea (AAD) in patients receiving intensive care with antibiotic monotherapy. I think this paper is well designed and well written. However, I think the manuscript needs major revision including statistical methods as follows:

Major comments:

1. I cannot understand why the authors excluded patients who received combined antibiotics therapy. I think it is better to include all patients who received antibiotics. The author should include all patients who received antibiotics or clearly explain the reason why they limited patients who received monotherapy only.

Response: Thank you for your comment. This study aimed to investigate the incidence of AAD and related factors in critically ill patients receiving antibiotic monotherapy, and these patients were the main focus of our research. Furthermore, this was a retrospective study with a small sample size. We hope to conduct a large-scale study on the combined

use of antibiotics and antibiotic monotherapy in the future. Therefore, in this study, we only included patients treated with single-use antibiotics.

2. Because protective effects of probiotics for AAD have been established, authors should consider use of probiotics as a confounding factor of the study. If the authors cannot evaluate probiotics use in the present study, the authors must clearly mention it as a limitation.

Response: Thanks for your suggestions. We have added the relevant descriptions at the end of the manuscript. The revised document has been submitted for your review.

3. The methods of multivariate analyses are unclear to me. Because the authors intend to evaluate predictive (risk) factors of AAD patients compared to non-AAD patients, logistic regression should be appropriate (because the objective variable is binary (non-contentious)). However, the authors mentioned performing multivariate regression analysis. If they performed multivariate regression, "odds ratio" should be "regression coefficient".

Response: Thank you for your opinions. We used univariate and multivariate logistic regression analyses to determine the factors related to AAD analysis. We apologize for the unclear description. We have corrected it in the manuscript.

4. Furthermore, odds ratio of age, ICU stay time, duration of antibiotics was less than 1.0, which means higher age, longer ICU stay, longer antibiotics use are protective factors of AAD! I think these results are inverted.

Response: Thank you for your reminding. We used logistic regression analysis to reanalyze the data and correct errors in the tables and manuscripts. The revised document has been submitted for your review.

5. According to above comments, I strongly recommend 1) re-evaluation using logistic regression analysis or 2) confirmation of "Odds ratio", "regression coefficient", and presence of inverted results.

Response: Thank you for your reminding. We used logistic regression analysis to reanalyze the data and correct errors in the tables and manuscripts. The revised document has been submitted for your review.

6. Because AAD patients are only 45, explanatory variables included in multivariate regression (such as logistic regression) should be 4-5 factors. The authors should mention the instability of regression model due to including too-much factors in limitation paragraph.

Response: Thanks for your suggestions. We have added the relevant descriptions at the end of the manuscript.

7. To improve the regression model, I suggest categorization of continuous variables.

Response: Thanks for your suggestions. We reanalyzed the relevant factors of AAD and updated the analysis results in the manuscript and table.

8. I think what the authors mentioned in “conclusion” is excessively expansion of the results. Statistical methods performed in the present study are association evaluation. “Association” is not always means “causal relationship” especially in “case-control study” such as the present study. For example, the association between longer ICU stay and higher proportion of AAD patients does not always mean that longer ICU stay causes AAD. Therefore, I do not think this study means that “ICU treatment time of patients should be shortened” to reduce AAD as the authors insist.

Response: Thank you for your reminding. In the "conclusion" section, we deleted the following statement: "ICU treatment time of patients should be shortened."

9. 2.1 Design, participants, and inclusion/exclusion criteria: “The study used a single-center retrospective design.” I think this study should be described as a case-control study because the authors evaluate factors associated with adverse outcome (i.e. AAD) by comparing cases with AAD to control cases (Non-AAD).

Response: Thank you for your advices. We revised the specified part as "The study used a single-center retrospective case-control study design."

Minor comments:

1. Abstract-conclusion: “longer ICU stay time ,” should be “longer ICU stay time,”

Response: Thanks. We made corresponding revisions in the manuscript’s “Abstract” section.

2. 1. Background: “AAD has become an important nosocomial infectious disease, especially in critically ill patients” AAD is not always infectious condition. The authors should replace AAD to CDAD or remove “infectious” in the sentence.

Response: Thank you for your advices. We deleted "infectious" in the sentence.

3. 1. Background: “condition[7]” should be “condition [7]”

Response: Thanks. We revised “condition[7]” to “condition [7]”in the manuscript.

4. a. Background: “Currently, research studies on AAD [8-10] found...” research and studies should be simply “researches” or “studies”.

Response: Thanks. We delete “research” in the manuscript.

5. 2.2.1 Diagnosis of AAD: The meaning of “smear of the stool has a dysbacteriosis or stool culture to detect pathogenic bacteria.” is unclear to me. If “stool culture to detect pathogenic bacteria.” means positive stool cultures, the causative agents should be mentioned in the “result” or any tables. Furthermore, I recommend to clearly define “dysbacteriosis”.

Response: Thanks for your suggestions. We have appropriately revised the description of AAD diagnosis in the "Diagnosis" section and clearly defined "dysbacteriosis." The revised document has been submitted for your review.

6. 4. Discussion “In our study, In our study,”: Please remove excessive “in our study”.

Response: Thank you for your reminding. We have deleted the excessive instances of “in our study” in the manuscript.

7. Basic disease and underlying diseases should be unified to “underlying diseases”

Response: Thanks. We revised it in the manuscript.

8. 4. Discussion “association analysis” is unclear to me. Specific method should be indicated here.

Response: We apologize for the unclear description. This should be “the multivariate logistic regression analysis” instead of “association analysis.” We have corrected it in the manuscript.

9. Table 2: I think it is better to p-values of the comparison of the proportion between AAD group and Non-AAD group in the table.

Response: Thank you for your suggestions. We have compared the p-values of both AAD and non-AAD groups in Table2.

We have updated the style of references according to the requirement of current journal. The revised document has been submitted for your review.

Thanks for your effort put on this manuscript. We look forward to hearing from you.

Yours sincerely

Litao Guo

April 9, 2020