Author’s response to reviews

Title: p53 expression in patients with ulcerative colitis - associated with dysplasia and carcinoma: a systematic meta-analysis

Authors:

Xiaohong Lu (luxiaohong_2017@163.com)
Yuanjie Yu (kpo0336644@sina.com)
Shiyun Tan (dtuo8852076@sina.com)

Version: 1 Date: 18 Jun 2017

Author’s response to reviews:

Response: p53 expression in patients with ulcerative colitis - associated with dysplasia and carcinoma: a systematic meta-analysis

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript (BMGE-D-17-00175). These comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections in accordance with approval. We have made all the required changes suggested by the editor and the reviewers. Please find our point by point response to all the inquiries as follows:

Editor Comments:

BMC Gastroenterology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Response: Dear Editor, thank you for your precious suggestions.
Reviewer reports:

Jun Sheng (Reviewer 1): Xiaohong and colleagues provided a meta-analysis for p53 expression in patients with ulcerative colitis - associated with dysplasia and carcinoma. This is an interesting paper with clinical significance. However, this paper needs minor revision.

Response: Dear Pro. Sheng, thank you for your approval and precious suggestions.

1. The major defect is that the author should define this paper as specific meta-analysis or system review. Because the paper includes studies with large heterogeneity, the type of this paper may be system review although some kind of meta-analysis is used in this paper.

Response: Dear Pro. Sheng, thank you for your precious comment. A meta-analysis was performed to mainly analyze the inconsistent and conflicting data of the included publications. Thus, a slight publication bias was found in UC with dysplasia versus without dysplasia or carcinoma (P = 0.025). And we also conducted a sensitivity analysis to evaluate the change of the pooled OR and heterogeneity by omitting an individual study. Our paper had been defined as “a systematic meta-analysis”, which was feasible, as described by these meta-analyses 1,2.

2. Due to the heterogeneity of enrolled studies, the authors need include subgroup analysis in addition to the ethnicity. That is, the authors should included novel aspects in this meta-analysis to reduce the statistic bias for the whole meta-analysis.

Response: Dear Pro. Sheng, thank you for your precious comment. Because other information was not very sufficient. Thus, we did not perform other available subgroup analyses. While, we added the statement of heterogeneity in Discussion section (Highlighting, Discussion section, Page 10, line 15-17).

3. The definition for "different types of UC is not so accurate. Does this definition stands for Mentreal Classification? Or the authors need to use other statement.

Response: Dear Pro. Sheng, thank you for your precious suggestion. We have revised this statement “different types of UC” as “different histological types of UC” in the manuscript (Highlighting, Introduction section, Page 5, line 5)

4. The language needs minor modification by English-native colleagues.
Response: Dear Pro. Sheng, thank you for your precious suggestion. I am very sorry for our imperfect writing. We read and revised the manuscript again to avoid vague words.

Julajak Limsrivilai (Reviewer 2): The study concept is good. This is the first meta-analysis to determine the association between p53 expression and the risk of dysplasia and cancer in patients with ulcerative colitis (UC). However, the meta-analysis of the association between KRAS and TP53 mutations with IBD-associated colorectal cancer has recently been published (Du L et al., Oncotarget 2017). Please find my comments below.

Response: Dear Pro. Limsrivilai, thank you for your kind approval and precious comments. Moreover, we also added the statement on this meta-analysis by Du et al. (Highlighting, Introduction section, Page 4, line 18-20).

1. The study by Vento et al. (ref. 16 in the manuscript) included 52 patients who underwent restorative proctocolectomy with construction of an ileal reservoir (42 patients with pouchitis, 10 patients normal ileoanal pouch), and 9 healthy subjects. The specimens in this study were ileal tissue and not colonic tissue. Should this study be included in the meta-analysis?

Response: Dear Pro. Limsrivilai, thank you for your precious comment. Please forgive us and we feel very sorry, we carefully read this study and previously extracted the data of UC group and normal tissue samples. While the purpose of our meta-analysis was to analyze the association between p53 expression and the risk of dysplasia and carcinoma in patients with UC. Thus, we removed this study and re-calculated the results.

2. The criteria to categorize the patients/tissues into each group in this meta-analysis is confusing. The tissues without dysplasia but from the patient with UC and dysplasia were categorized as UC without dysplasia group in some studies (e.g. Friis-Ottessen et al., ref. 14 in manuscript), but were categorized as UC with dysplasia in the study by Sato et al. (ref. 25 in manuscript). Please kindly clarify this issue.

Response: Dear Pro. Limsrivilai, thank you very much for your precious suggestion. Please forgive us, we carefully read this study by Friis-Ottessen et al.. We found some undefined types of UC in this study. Therefore, we finally removed this study by Friis-Ottessen et al.. And we recalculated the results. Other studies satisfied our study selection.
3. The authors stated that the literature search was performed up to February 13th, 2017. However, some studies may have been missed. Some examples are among the studies below.


Could the authors kindly provide the reasons for excluding these studies?

Response: Dear Pro. Limsrivilai, thank you very much for your nice comment. We carefully read these two publications. The study only reported the results of p53 expression in UC with dysplasia by Wong et al. Ilyas et al. reported that 10 resected colorectal specimens from patients who had had a biopsy positive for dysplasia in terms of p53 expression. Therefore, these studies were excluded based on insufficient data.

4. The authors did not include the studies which included both Crohn's disease and ulcerative colitis patients in this meta-analysis. The data would be more complete if the authors can obtain more information specifically for UC patients in those studies and include them in this meta-analysis. One example is the following study.


(20 of 31 IBD patients with colorectal cancer had UC)

Response: Dear Pro. Limsrivilai, thank you very much for your nice suggestion. Because the eligible studies on p53 expression and IBD were three, including a small population. Thus, we did not evaluate the association between p53 expression and different histological types of IBD. In addition, we also added the relevant statement in limitation section (Highlighting, Discussion section, Page 11, line 12-15).

5. In the search strategy section, Boolean operators in the search term, such as AND and OR, should be entered in uppercase letter.
Response: Dear Pro. Limsrivilai, thank you very much for your nice comment. We have revised the search term by highlighting (Methods section, Page 5, line 14).

6. I do not understand how the authors interpreted the results of sensitivity analysis in the section 3.5. To the best of my knowledge, sensitivity analysis is performed to investigate the validity and robustness of the meta-analysis. There are 2 main methods.

1. Applying the meta-analysis to subsets of studies based on high-quality versus low-quality studies, early studies versus late studies, and etc.

2. Applying the leave-one-out method

In this meta-analysis, the authors stated in the Method section that they used the leave-one-out method, which is done by performing a meta-analysis on each subset of the studies obtained by leaving out exactly one study. Thus, there should be 12 meta-analyses in the sensitivity analysis in UC with dysplasia vs. without dysplasia or carcinoma (the same numbers as the numbers of studies included in the meta-analysis comparing UC with dysplasia vs. UC without dysplasia or carcinoma). If the results of each meta-analysis in these 12 meta-analyses are consistent, then there is confidence that the overall meta-analysis is robust and not dependent on any single study.

However, in the Results section, the authors reported the results of sensitivity analysis by reporting the result of only one meta-analysis with removal of the study by Klump et al.. This looks like the way to report the results when sensitivity analysis is done by the 1st method. In this case, the authors should have stated the criteria of selection or removal of the studies for the sensitivity analysis.

Response: Dear Pro. Limsrivilai, thank you very much for your precious suggestion. Indeed, a sensitivity analysis was conducted to determine the change of the pooled OR and heterogeneity by omitting an individual study. A same manner of a sensitivity analysis was analyzed in other meta-analysis 3. Additionally, we have added the relevant reason on the removal of the study by Klump et al. (Highlighting, Discussion section, Page 10, line 15-17).

7. I would like to see the grading of quality of the studies included in this meta-analysis.

Response: Dear Pro. Limsrivilai, thank you very much for your good comment. We have added the quality assessment of the included studies in our manuscript (Highlighting, Methods section, Page 6, line 9-11; Results section, Page 7, line 11-12).
Editorial Policies

Declarations
- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

Response: Thank you for your precious suggestions. The above information has been revised by highlighting in our manuscript (Declarations section, Page 12, line 12, line 21).

We tried our best to improve the content of the manuscript and made some changes in this manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked by highlighting or red in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

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

Yours sincerely,

References
