

Dear Editor,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "*Microbiome Changes in Gastric Mucosa and Gastric Juice in Different Histological Stages of Helicobacter Pylori-Negative Gastric Cancers*" (No. 73407). We have studied the comments carefully and have revised our manuscript which we hope meet with their approval.

Point-by-point replies are listed below.

We hope that this revised version is acceptable for publication in *World Journal of Gastroenterology*. We are looking forward to hearing from you soon.

Best Regards,

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No. 73407

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The article is in generally well done. 1- The manuscript adequately described the background, presented status and significance of the study. 2- The manuscript described Materials and methods (e.g., Study Design and Participants, Sampling and Histological Evaluation, DNA Extraction and 16s rRNA Gene Sequencing, 16S rRNA Gene Sequencing Data Processing, Bioinformatic Analysis, Network Analysis of core microbes and Data Analysis, etc.) in adequate detail. 3- The research objectives are achieved by the experiments used in this study. This study selected 56 SG, 9 AG, 27 IM, 29 Dys and 13 GC with H. pylori negative to explore gastric microbiome dysbiosis across stages of HPNGC and the difference of bacterial communities between gastric mucosa and juice. 4- The manuscript interpreted the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. 5- Manuscript included sufficient, good quality Figures and Tables. 6- The manuscript cited appropriately the latest, important and authoritative references in the introduction and discussion sections. However, the format of the references needs to be revised. 7- The manuscript is well, concisely and coherently organized and presented and the style, language and grammar are accurate and appropriated. However, further editing and proofreading are needed to maintain the best sense of reading.

Response

We very much appreciate those helpful comments. The format of the references has been carefully revised. All the language and grammar in the manuscript have been rechecked sentence by sentence. We have rechecked our data and figures after careful editing and sent our revised manuscript to a professional English language editing company to polish the manuscript further.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This study is a retrospective analysis that focused on investigating the gastric microbiome dysbiosis across stages of HPNGC and the

difference of bacterial communities between gastric mucosa and juice. This study contains merit for advancing the therapy of gastric cancer and the illustrations help the readers to make a more understanding of the study; however, some concerns have been noted including: 1. Please add a structured abstract according to the required format and it should show a summary of the content of your manuscript. 2. If possible, it is best to add the brands of reagents and instruments used in the Materials and Methods. 3. The format of references should be modified. Otherwise, this is a very good paper and CAN BE CONSIDERED FOR PUBLICATION. Regards

Response

We greatly appreciate this helpful comment.

1. We thank the reviewer very much for raising this meaningful issue. We have written an Abstract and uploaded it in the submission system. Besides, according to the requirement of editor, we added Article Highlights to provide a concise introduction to our study.
2. Thank you very much for pointing out this question. In our study, DNA extraction was use the E.Z.N. A® Soil DNA Kit (Omega Bio-tek, Norcross, GA, USA). The experimental procedures were followed by the manufacturer's instructions. We clarified this in the revised manuscript.
3. The format of references had been modified.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript is focused on H. pylori negative patients and determined gastric microbiome dysbiosis across stages of HPNGC and the difference of bacterial communities between gastric mucosa and juice. The designed of the study is very good, the biopsy specimens and gastric juice were obtained from patients during upper gastroenterology endoscopic examination or ESD due to precancerous mucosal lesions. They performed 16S rRNA gene analysis of gastric mucosal and juice samples and bioinformatic analyses. The results are

excellent, data of 134 H. pylori negative patients has been well analyzed. They found that in the negative phase of H. pylori, the structure of the gastric microbial community changes along the SG-AG-IM-Dys-GC stage, and the bacterial community of gastric juice differed from that of the gastric mucosa, and HPNGC and its precancerous lesions have distinct bacterial taxa. This is essential for readers to understand the correlation between the diversity of gastric microbiota and the development of gastric cancer. I recommend accepting this manuscript for publication after a minor editing.

Response

We greatly appreciate these helpful comments. We have rechecked our data and figures after careful editing and polished the language of our manuscript further.