Dear Editor:

We sincerely thank the editor and all reviews for thoroughly reviewing our manuscript, and those comments are all very valuable and helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. The reviewer comments are laid out below in italicized font and specific concerns have been numbered. Our response is given in the normal font and the amendments are highlighted with yellow color in the revised manuscript.

Here are our point-by-point responses:

Reviewer #1:

Scientific Quality: *Grade B (Very good)*

Language Quality: *Grade A (Priority publishing)*

Conclusion: *Minor revision*

Specific Comments to Authors:

HP infection is one of the most common and actively studied bacterial infections in the world. Today we consider HP as the leading etiological factor of chronic gastritis and a class 1 carcinogen in relation to the risk of developing gastric cancer. However, in relation to other diseases with localization outside the stomach, the role of HP infection appears to be extremely controversial. In this regard, the article submitted for publication is very relevant. At the same time, I would like to invite the authors to make a number of clarifications Selection of literature. It seems extremely important to describe in detail the procedure for selecting sources included in the work (by what search words, in what databases, what criteria were used to select) Modulation of the intestinal microbiota induced by HP infection is an important potential factor in increasing the risks of colorectal cancer and polyps. I propose to present this section in more detail. The results of numerous epidemiological and clinical studies regarding the connection between HP and the risk of colorectal cancer have not yet reached consensus, and therefore I suggest that the authors report not on the connection, but on the association until the connection is finally proven

Answer 1. Thank you very much for your suggestions. We have added supplementary information regarding the Selection of literature in the manuscript as follows: “In this paper, two researchers (DQ-Y and Y-L) conducted independent literature searches using PubMed, Embase, and Cochrane Library databases to obtain more comprehensive literature data. The search was conducted from inception to December 2023, with search keywords including “Helicobacter pylori”, “H. pylori”, “Helicobacter pylori infection”, “H. pylori infection”, “colorectal polyp”, “CP”, “colorectal adenomatous polyp”, “CAP”, “colorectal adenoma”, “colorectal neoplasm”, “colorectal neoplasia”, “colorectal cancer”, “colorectal carcinoma”, “CRC” and “colorectal tumor”. Additionally, manual searches of the reference lists of the obtained articles were conducted to avoid any omission of studies.

We hope you will be satisfied with our supplement.

Answer 2. Thank you very much for your suggestions. Based on your suggestions, we have made the following modifications (additions are highlighted with a yellow background):

"Chronic H. pylori infection is a major cause of diminished microbial diversity in the stomach[71]. It also boosts the number of microorganisms in stomach cancer, including nitrate-reducing bacteria, nitrosylobacteria, and Escherichia coli, which promotes nitrate metabolism. The resultant N-nitroso compounds function as carcinogens and promote tumorigenesis[72].An increasing body of evidence suggests that H. pylori infection also impacts the intestinal flora. H. pylori invasion of the intestinal mucosa may lead to reduced intestinal permeability[72] and inhibit Escherichia coli DNA[73]. H. pylori may also trigger host immune responses, thereby altering the intestinal flora[74, 75]. Furthermore, long-term H. pylori infection can alter the pH in the stomach, enabling more microorganisms to overcome the acid barrier and enter the distal intestinal tract[75]. CagA also can stimulate the overproliferation of intestinal stem cells and alter the host microbiota[76].Recent study has revealed that H. pylori promotes the enrichment of Akkermansia spp. and Ruminococcus spp., which breakdown intestinal mucus, in the colon tissue of H. pylori-infected mice, resulting in a pro-inflammatory and pro-carcinogenic microbiota signature[11]. It is possible that H. pylori infection weakens the intestinal barrier. Furthermore, Luo et al.[77] discovered that in the early stages of CRC development, H. pylori infection promotes the amplification of temperate phages to disrupt intestinal virome homeostasis and interacts with bacterial communities to target tumor-associated bacteria such as Lactobacillus[78] and Enterococcus faecalis[79], promoting the development of CRC in mice. To summarize, H. pylori-induced intestinal flora dysbiosis is a significant risk factor for the development of CRC."

We sincerely hope the supplement could be acceptable for you.

Answer 3. We really appreciate your valuable advice. We have removed the similar reports, such as "However, the results of numerous epidemiological and clinical studies have not yet reached a consensus.". In addition, we have made the following supplementary changes based on your suggestions: "In recent decades, the connection between H. pylori and colorectal polyp (CP) or CRC has sparked attention. And, there is accumulating clinical and basic experiment evidence indicating that H. pylori infection is a risk factor for CP/CRC and promotes the development of CRC."

We sincerely hope the supplement could be acceptable for you.

Reviewer #2:

Scientific Quality: *Grade B (Very good)*

Language Quality: *Grade B (Minor language polishing)*

Conclusion: *Minor revision*

Specific Comments to Authors:

The authors should expand on the following • The authors should provide appraisals whether the editorial effectively addresses the conflicting results from previous clinical studies and Mendelian studies regarding the association between H. pylori and colorectal polyps/cancer? • Are the potential sources of inconsistency explored and discussed?

Answer 1: Thank you very much for your questions and suggestions. **Answer 1.1.**We have only discovered the conflicting results from previous clinical studies regarding the association between H. pylori and colorectal polyps/cancer, through a review of numerous literatures. And, we have provided an objective description of the conflicting results without dwelling extensively on the contradiction or offering detailed solutions. **Answer 1.2.** In addition, through a literature review and comparison of methodological differences and outcomes among various studies, we considered factors such as the criteria for positive H. pylori infection, the diagnostic methods of H. pylori, the interference of H. pylori-related diseases, incomplete colonoscopy, sample size and age, as well as the differences of ethnic and regional environmental, which may have contributed to the conflicting results.

We hope our answer will satisfy you.

• How robust is the predictive model developed by Zhang et al., and what are its clinical implications?

• Are the limitations of the predictive model acknowledged, and suggestions for improvement provided?

Answer 2： Thank you very much for your questions and valuable advice. **Answer 2.1.** Through the calculation of calibration curves, receiver operating characteristic(ROC) curves, and decision curve analysis (DCA) curves, Zhang has demonstrated that the column-line graph prediction model has strong calibration, discrimination, and prediction abilities in predicting the risk of H. pylori infection. The preliminary consistency of the results between the detection cohort and the validation cohort suggests that the model has good robustness. However, due to factors such as small sample size and single-center data, the predictive model is still needed for validation and improvement. **Answer 2.2.** The prediction model is used to predict the risk of H. pylori infection after intestinal polypectomy, and identify individuals at high risk of Helicobacter pylori infection. **Answer 2.3.** In the "5. Conclusions and translational implications" section, we have described the limitations and shortcomings of the column-line graph prediction model and provided some constructive suggestions: 1. Future studies should focus on adjusting important confounding factors such as age, metabolic factors, smoking, alcohol consumption, physical activity, diet, racial differences, socioeconomic status, and the use of antibiotics. 2. The study should also focus on the relationship between the time of H. pylori infection or recurrence after

post-colon polyp surgery and the CAP. 3. Multi-center, large-scale prospective studies should be conducted to develop a scientific and rigorous H. pylori-CRC screening program. 4. More attention should be paid to the joint detection of CAP and H. pylori-related diseases or specific diseases. These suggestions appear to be capable of refining the model and increasing the screening rate and diagnostic accuracy for individuals at high risk of H. pylori infection.
We sincerely hope the answers could be acceptable for you.

In all, I found the comments of editor and reviewers are quite helpful and valuable, and I revised my paper point-by-point. We hope our revised manuscript could be acceptable for you. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help.
Thank you and the review again for your help!

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Thank you very much.
Sincerely,
Dr Yan Jiao