Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript. We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for you and Reviewers' warm work earnestly, and hope that the correction will meet with approval. Best wishes to you.
Sincerely,
Feng Gao

The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1:

Dear Reviewer:

Thank you very much for your comments. Those comments are very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction. We appreciate for your warm work earnestly, and hope that the correction will meet with approval. Thank you very much for your comments and suggestions again. Best wishes to you.

1. There is no healthy control group as the control group here had also GI symptoms, which is the biggest problem causing significant trouble in analysing the results. Especially, considering the H.pylori findings and the epidemiology.

Response: This study is a retrospective study. The celiac disease group is compared with the non-celiac disease group. Due to the limited conditions, there is no healthy control group. Your comments are indeed very helpful to our research. We will refer to your comments to further conduct a multi-center study including healthy control groups. We limited the infection of Helicobacter pylori to people with gastrointestinal symptoms, and explained it in the article.

2. The authors conclude in the abstract that there is a high incidence of celiac disease in China. However, the patients had all gastrointestinal symptoms causing significant bias in the numbers. The manuscript should be corrected and say that the incidence and prevalence was XX% in patients with gastrointestinal symptoms. In patients with GI symptoms I would not say that these numbers are high. Now the manuscript is misleading.

Response: We have re-written this part according to your suggestion (Page 3).

3. Introduction, second sentence: Celiac disease antibodies are not the main cause of small-bowel damage in celiac disease, the main cause are the T-cells in the mucosa.

Response: We have made correction according to your comments (Page 4).

4. The authors should present epidemiological data from patients with symptoms.

Response: We provide it in the attachment..

5. Second chapter, introduction: Remove the sentences on AGA, it is not needed here as it is not studied. Also, it is not used anymore in celiac disease as the authors mention.

Response: We have modified it according to your comments (Page 5).

6. Genetics are poor for diagnostics as there are present in most of the population, it should mentioned in the introduction specifically.

Response: We have modified it according to your comments (Page 5).

7. anti-ttg is the choice for screening but Ema is widely used for confirmation in celiac disease.

Response: We have modified it according to your comments (Page 5).

8. Duodenal mucosa may not be the golden standard for celiac disease much longer. In children ttg+ema is sufficient (ESPGHAN guidelines for celiac disease) and also in adults the results are similar and guidelines are changing: Fuchs et al. "Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities" Aliment Pharmacol Ther. 2019 and Penny et al. "Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts" Gut 2021.

Response: Because our laboratory has not yet carried out serum EMA testing, the diagnosis is still based on the previous diagnostic criteria for celiac disease, that is, pathological examination. We will pay close attention to the latest changes of the guidelines.

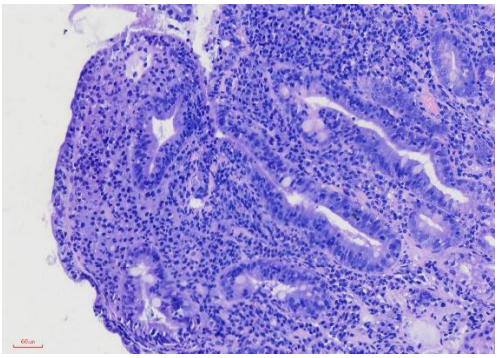
9. Methods, endoscopic assessment: Did you take the duodenal bulb and and descending duodenal biopsies in separate containers? It has been shown that H.pylori affects especially duodenal bulb causing false positive findings in bulb samples (Taavela et al. "A Prospective Study on the Usefulness of Duodenal Bulb Biopsies in Celiac Disease Diagnosis in Children: Urging Caution" AJG 2016). Bulb has also lower villous height crypt depth values than descending duodenum.

Response: These tissues are stored in different containers. Each time we take a specimen, we change the container.

10. Figure 2D is not readable and should not be used for diagnostics. The orientation of the sample is poor that can result to false diagnoses.The crypts must be longitudinal in order to assure the correct cutting of the villi. Correct the figure 2D and see the papers by Taavela et al. "Validation of morphometric analyses of small-intestinal biopsy readouts in celiac disease" Plos One 2013 and Ravelli&Villanacci "Tricks of the trade: How to avoid histological Pitfalls

in celiac disease." Pathol Res Pract. 2012. - Also, the Marsh grade should not be evaluated above Brunners glands as seen here as the villous height can be lower above brunner glands. See the above paper by Taavela et al. in AJG 2016 and Chang et al. "Pathological and clinical signifi cance of increased intraepithelial lymphocytes (IELs) in small bowel mucosa." APMIS 2005

Response: Thank you very much for your valuable suggestions. We have examined the pathological sections of all patients diagnosed with CD and corrected the pictures in the article. Considering that the second reviewer suggested deleting them, we put them in the attachment. We admire your solid professional foundation (Support figure).



11. Section on H.pylori results: H.pylori infection is the cause for duodenal lymphocytosis and duodenal architecture damage explaining why duodenal damage is more pronounced in these patients! This is a very interesting finding!

Response: Thank you for your recognition of the findings in this research.

12. In the discussion, chapter three, the sentence on screening is odd. In Britain (as in all Europe), it is suggested to screen the relatives of celiac disease patients and those with other autoimmune diseases. Mass screening of celiac disease is not at the moment recommended. I believe the recommendation should be the same in China. If only the patients with GI symptoms are tested, most of celiac disease patients are missed as most new celiac disease patients in Europe present with extraintestinal manifestations or are those screened in-at risk groups such as relatives and patients with other autoimmune diseases, see for example study by Zingone et al. “Clinical features and psychological impact of celiac disease at diagnosis” in Dig Liver Dis. 2021.

Response: We have made correction according to your comments (Page 11).

13. In discussion, chapter four, the chapter is very speculative in terms of discussing the findings. The authors presume that H.pylori could cause celiac disease. Such finding can not be made on this retrospective data. The most obvious cause is H.pylori causing duodenal damage in addition to celiac disease in these patients. Also the discussion is controversial as the authors say that H.pylori negative patients have less antigens in duodenum and thus less autoimmune disease but then the H.pylori eradication causes more celiac disease?? Please

refrain from too much speculation on the topic as the data does not support such speculations. - See paper by Taavela et al. “A Prospective Study on the Usefulness of Duodenal Bulb Biopsies in Celiac Disease Diagnosis in Children: Urging Caution” Am J Gastroenterol. 2016. In this paper helicobacter pylori among others caused duodenal damage in non-celiac patients.

Response: We have made correction according to your comments (Page 11).

14. The last chapter in discussion. The authors begin by discussing latent CD, but the switch oddly to the need of repeating endoscopy and cancer? In Europe, repeat endoscopy is not considered a necessity though mentioned still in the guidelines. Please see: Pekki H, Kurppa K, Mäki M, et al. ”Performing routine follow-up biopsy 1 year after diagnosis does not affect long-term outcomes in coeliac disease” Aliment Pharmacol Ther. 2017 and Al-Toma et al. “European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders” United European Gastroenterol J. 2019

Response: We have made correction according to your comments (Page 11).

15. The authors say that the mortality in celiac disease has risen?? I disagree. Celiac disease patients have lower or similar mortality as non-celiac disease patients. See Koskinen et al. “Overall and Cause-Specific Mortality in Adult Celiac Disease and Dermatitis Herpetiformis Diagnosed in the 21st Century” Am J Gastroenterol. 2020.

Response: We have made correction according to your comments (Page 12).

16. I believe that overall the discussion on repeat endoscopy and mortality in celiac disease is not needed here as the authors have focused on CD epidemiology, clinical presentation and h.pylori and not follow-up in their own study. Thus, I suggest to remove these. The discussion on latent CD and the need for wider screening in China would be interesting.

Response: We have made correction according to your comments (Page 12).

17. In conclusions, please specify that these were patients GI symptoms so the prevalence does represent true population. -Also, the authors must report that the GI manifestations were similar in all regions, but other manifestation (extraintestinal, asymptomatic) were not studied. - This is too speculatice for a conclusion: “Pathological improvement in CD patients with serological improvement after H. pylori treatment are needed to confirm this association.”

Response: We have made correction according to your comments (Page 13).

18. Table 4 is not needed, the number are too low and the data is not clinically interesting.

Response: We have deleted table4 according to your comments. Special thanks to you for your good comments. Thank you.

Reviewer #2:

Dear Reviewer:

Thank you very much for your comments. Those comments are very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction. We appreciate for your warm work earnestly, and hope that the correction will meet with approval. Thank you very much for your comments and suggestions again. Best wishes to you.

INTRODUCTION - “An increase in celiac-specific autoantibody levels can lead to varying degrees of damage to the small intestinal mucosa….”. Here, I may understand that there is direct pathogenic link between the autoantibody and the specific tissue damage. Of course, there is a correlation, but I would ask the authors to double check this statement and possibly rephrase it. - In general, I suggest revising the English writing

Response: We have modified it according to your comments and retouched this article*. Thank you (Page 4).*

- second paragraph: I do not think all this specific information about each specific CD autoantibody is necessary to introduce this study. I recommend the authors shorten it.

Response: We have made correction according to your comments (Page 5).

- third paragraph: same considerations as above. Actually, some concepts of this paragraph may be better suitable to the discussion. - the authors should support the epidemiological background of CD in Asia and, in detail, in China and surrounding areas, with appropriate and recent references, which indeed emphasizes the limited amount of information in this regard, but not completely absent (Medicina (Kaunas). 2019 Jan 12;55(1):11. doi: 10.3390/medicina55010011; J Dig Dis. 2021 Sep 5. doi: 10.1111/1751-2980.13049. Online ahead of print)

Response: We have made correction according to your comments (Page 4).

MATERIALS AND METHODS

- the ethical statement should not be put at the end of the section or in a dedicated subsection. Please, specify the number and date of the IRB approval, as well as the type of informed consent.

Response: We have made correction according to your comments (Page 6).

- what is “electronic” gastrointestinal endoscopy?

Response: We have made correction according to your comments (Page 6).

- the authors should describe schematically and clearly the inclusion criteria in the first section. Also, clarify if this study includes both adults and children.

Response: We have made correction according to your comments (Page 6).

- Table 1 must be part of the results…and therefore should be probably table 2. Table 1 should be the one reporting the demographic characteristics.

Response: We have made correction according to your comments (Page 8).

RESULTS

- the age distribution is missing In the “epidemiological characteristics”.

Response: We have made correction according to your comments (Page 8).

- again, the English writing should be extensively and professionally revised.

Response: We have made correction according to your comments.

- I am not sure if figure 2 is important since it does not add anything new. I think it can be removed.

Response: We have deleted figure 2 according to your comments.

DISCUSSION

- I would suggest the authors to list their main findings clearly and schematically. Of course, the first point is the epidemiological aspect (CD in patients with GI complaints) in China, also according with different ethnicities, and second the interesting analysis of the association with HP infection. Then, they should discuss these points one by one through the appropriate medical literature, without mixing them.

Thank you very much for your valuable suggestions. We have listed the incidence of CD and the differences between CD and non-CD patients in this study on the incidence of CD and the differences in HP infection between CD and non-CD patients in table3. We also further searched the literature and discussed them(Page 10).

- “The European region is often considered as the origin place of CD” .Can you explain and clearly support this statement or otherwise revise it?

Response: We have made correction according to your comments (Page 10).

- As for the ethnicity-related discussion, the authors state “HLA-DQ2 and HLA-DQ8 gene carrier rates are high in Kazakhs and Uyghurs [11]”. However, this reference is specifically related to the minorities in China, which is not clearly specified by the authors. Indeed, there are recent original article clearly demonstrating and describing this aspect for these ethnicities in general, at least for Kazakh population (refer to: PLoS One. 2020 Jan 2;15(1):e0226546. doi: 10.1371/journal.pone.0226546) as I actually understand by this statement. As regards Uyghurs, there is a recent original paper (Aliment Pharmacol Ther. 2020 Jun;51(11):1116-1129. doi: 10.1111/apt.15737) but, again, it refers to this ethnicity in China; anyway, this paper should be used to support this specific point, in my opinion.

Response: We have made correction according to your comments (Page 10). Thank you very much.

- discuss better the clinical aspects (e.g. age or typical/atypical ratio, etc.) compared to other populations, where the epidemiology and clinical characteristics of CD are much better defined.

Response: We have made correction according to your comments (Page 10,11).

- “The gut microbiota plays an important role in regulating intestinal immunity, and H. pylori is the most common cause of inflammation in the upper gastrointestinal tract.” First, this sentence lacks any supporting reference; second, I would not mix the concept of HP infection with the aspects of the microbiome. Please, carefully revise this paragraph.

Response: We have made correction according to your comments (Page 11).

- Indeed, also the sentence “However, we believe that this association may be related to the genetic factors of CD and/or H. pylori, the virulence of H. pylori, and the immunopathology involved.” is questionable because the authors do not provide any explanation for their belief. If this is not possible, I would suggest removing it. Anyway, this is a pure epidemiological and clinical study, even retrospective, I recommend avoiding mechanistic considerations and, conversely, to focus the discussion on the aspects highlighted at the beginning of the introduction and in my previous comments.

Response: We have re-written this part according to your suggestion (Page 10, 11).

CONCLUSION

- “A high incidence of CD was observed in Northwest China.” Incidence or prevalence? Moreover, please provide the percentage by specifying your study population. - please, clarify better the conclusion related to HP and CD.

Response: We have made correction according to your comments(Page 13).

- The conclusion should be completely revised in my opinion. REFERENCES - to be updated and completed based on the specific discussion points, according to the previous comments.

Response: We have modified it according to your comments. Once again, thank you very much for your comments and suggestions.