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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 71548

Title: Epidemiological, clinical, and histological presentation of celiac disease in Northwest China

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03307766
Position: Editorial Board
Academic degree: MD, MSc, PhD
Professional title: Associate Professor, Director, Doctor
Reviewer's Country/Territory: Kazakhstan
Author's Country/Territory: China

Manuscript submission date: 2021-09-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-12 12:44

Reviewer performed review: 2021-09-18 11:39

Review time: 5 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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 - 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. - 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) 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. - what is "electronic" gastrointestinal endoscopy? - the authors should describe schematically and clearly the inclusion criteria in the first section. Also, clarify if this study includes both adults and children. - 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. RESULTS - the age distribution is missing In the "epidemiological characteristics". - again, the English writing should be extensively and

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professionally revised. - I am not sure if figure 2 is important since it does not add anything new. I think it can be removed. 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. - "The European region is often considered as the origin place of CD,…" Can you explain and clearly support this statement or otherwise revise it? - 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. - 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. - "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. - Indeed, also the sentence "However, we believe that this association may be related to the genetic factors of CD and/or H. pylori, the

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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. 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. - 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.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05261106
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Finland

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Here are my comments regarding the manuscript by Wang et al. entitled "Epidemiological, Clinical, and Histological Presentation of Celiac Disease in Northwest China". The paper focuses on celiac disease prevalence, presentation and the role of helicobacter pylori in these patients. Data from China is lacking and thus the topic is important. English is good and the language is fluent. However, the study has some problems, below are my comments point by point: 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. 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. 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. 4. The authors should present epidemiological data from patients with symptoms. 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. 6. Genetics are poor for diagnostics as there are present in most of the population, it should mentioned in the introduction specifically. 7. anti-ttg is the choice for screening but Ema is widely used for confirmation in celiac disease. 8. Duodenal mucosa may not be the golden standard for celiac disease much

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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. 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. 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 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! 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

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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. 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.

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 15. The authors say that the mortality in celiac disease has risen?? I disagree. Celiac disease patients have lower or similar mortality as

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

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 71548

Title: Epidemiological, clinical, and histological presentation of celiac disease in Northwest China

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05261106
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Finland

Author's Country/Territory: China

Manuscript submission date: 2021-09-12

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2022-01-04 13:02

Reviewer performed review: 2022-01-04 13:18

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [ ] Anonymous [Y] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear authors, I accept your answers to my comments, the article is now much better, I have no more comments.

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Position: Editorial Board

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Overall. the authors addressed my main points. Some grammar/typing inconsistencies can be addressed in the proof correction.