ROUND 1

Manuscript Title:

Understanding celiac disease monitoring patterns and outcomes after diagnosis: a multinational retrospective chart review study

Dear Reviewers,

Thank you for your thoughtful review and feedback on our submitted manuscript. We have gone through the comments and provided our responses in the table below. We hope you will find the revised manuscript suitable for publication in World Journal of Gastroenterology.

Reviewer 2			
Scientific Quality: Grade D (Fair) **Language Quality:** Grade A (Priority publishing) **Conclusion:** Major revision **Specific Comments to Authors:** In this descriptive retrospective chart review study authors present monitoring patterns of follow up in three countries based on sample of 300 patients. Multicentric design and hundreds of patients are strengths of the study. However, in the view of recent published guidelines for the celiac disease (CD) (Al-Toma 2019) the practical outcomes from the study are not too clear. Authors described basic clinical and demographic characteristics of the cohort and its changes through the follow up. The conclusion that follow up of CD patients is not optimal without any analysis of contributing factors is quite simple. I am afraid that such information is not innovative for readers. Standardized histopathology classification according to Marsh and Oberhuber is usually used for description of duodenal atrophy – but not in this study. Answers to some questions may improve the quality of this study and can bring more interesting results.			
1	Materials and Methods	How were patients´ records selected for evaluation? It is probable that 100 patients from each center are not all registered patients with CD and I assume that authors had some key how to select them. Was this key the same for all centers?	Yes, all sites were instructed to identify eligible patients if they had biopsy-confirmed celiac disease, were diagnosed with CD between 2008 and 2012 and had at least one follow-up visit before Dec 31, 2017. All the site investigators used following approach – using database of all patients at the site, eligible patients were first identified based on date of diagnosis. Identified those were eligible from this list starting with those

			diagnosed in 2012 and consecutively backwards from that date (until diagnosis date in 2008) and the first 100 eligible patients were included. The instructions regarding selection of consecutive patients was explicit for all sites to avoid selection bias. This has been clarified in the methods section.
2	Materials and Methods	From this view, it is probably impossible to compare characteristics among countries. Are there any parameters that are included in „standard“ follow-up visit in each country? Are they different?	Standard parameters assessed across all sites include celiac serologies (although the frequency of retest is very heterogeneous), symptoms, gluten free diet adherence and nutritional values. The major test where there is some discrepancy between sites is in follow up endoscopy/biopsy and this is noted as a limitation in the discussion section.
3	Results	What was the proportion of abnormal results of densitometry? How it changed the management?	The study did not collect results from the bone densitometry performed; the purpose was to understand how many patients underwent this procedure during the follow-up period (following diagnosis). Would also note that as DEXA is not performed in the gastroenterology unit, results of these tests were not routinely available. This has been added to the results section.
4	Materials and Methods / Results	No data regarding used serology tests for diagnosis and / or follow up are presented. I am missing any fact about follow up serology either positive or negative test and relation to clinical symptoms and atrophy. These data might be included in the medical records and such analyses may improve the message from this study. Serology follow up is recommended generally.	We do have data on serology test results at diagnosis and follow-up (for each test, results were categorized as high, normal, low or unknown). The number of available serology tests is much lower during follow-up than is available at diagnosis. This information is now presented in a supplemental table and referenced in the results section.

		Presence of atrophy alone without exclusion of other causes of atrophy may lead to misdiagnosis.	
5	Materials and Methods / Results	I can recommend trying to analyse why were some patients lost from follow up. This may be the practical point to focus on. Was the next appointment recommended during the initial visit? Is it non - compliance or absence of recommendation or other factors?	We did collect details on last recorded follow-up with the patient – which could be either discharged, referral made to specialist, scheduled next follow-up visit with patient, other, unknown. This information has been added to the results section.

Editorial Office – Science editor

1 Scientific quality: The manuscript describes a retrospective cohort study of the multinational chart review in celiac disease. The topic is within the scope of the WJG. (1) Classification: Grade C and Grade D; (2) Summary of the Peer-Review Report: This study is interesting, however some points deserve further details of clinical relevance. The conclusion that follow-up of CD patients is not optimal without any analysis of contributing factors is quite simple. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 1 figure. A total of 15 references are cited, including 3 references published in the last 3 years. There are no self-citations.
2 Language evaluation: Classification: Grade A and Grade B.
3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the STROBE checklist, and the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was found in the Bing search.
4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Takeda Pharmaceuticals. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG.
5 Issues raised: (see below)
6 Re-Review: Required
7 Recommendation: Conditionally accepted.

1	General	I found no “Author contribution” section. Please provide the author contributions	We have now added the author contributions section.
2	General	I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)	Not applicable
3	General - Figures	I found the authors did not provide the	We have provided the original figures in the revised

		original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor	version of the manuscript.
4	Highlights	I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.	We have now added a section on “article highlights”.

ROUND 2

Manuscript ID:

60615

Manuscript Title:

Understanding celiac disease monitoring patterns and outcomes after diagnosis: a multinational retrospective chart review study

Dear Reviewers,

Thank you for your thoughtful review and feedback on our submitted manuscript. We have gone through the comments and provided our responses in the table below. We hope you will find the revised manuscript suitable for publication in the World Journal of Gastroenterology.

Action number	Section	Reviewer comment	Author response/change in manuscript
Reviewer 1			
Scientific Quality: Grade B (Very good)			

Language Quality: Grade A (Priority publishing)
Conclusion: Accept – general priority
Specific Comments to Authors: This is well designed, performed and written retrospective cohort study for the evaluation of monitoring patterns and outcomes after diagnosis of celiac disease in three gastroenterology referral centers in UK, United States and Norway. The authors investigated altogether 300 patients with biopsy-confirmed celiac disease who were followed-up for a mean of 29.9 months. The authors give a sufficiently clear overview about the study background and raised clearly the aim of the study, which is fulfilled. The statistical analysis was specified sufficiently well. The material studied is large enough and allows to drawn the conclusions. The Results are presented clearly and have been discussed well. The paper is supplied with 3 Tables and one Figure which give very good overview about the results and are presented very clearly and correctly. The authors found that during the follow-up 68.4% of patients were recorded as having ongoing gastrointestinal symptoms and 36.6% had continued villous atrophy. The authors suggest that more routine follow-up assessment of celiac disease activity is needed. This paper has important clinical outcome because pay attention on the relevance of monitoring of villous atrophy, used in combination with adjunctive pharmacologic therapy in improvement of outcomes in patients with celiac disease. However, I will suggest to add and underline in conclusion some country/site-specific differences evaluated during this world-monitoring study.

1	General	I will suggest to add and underline in conclusion some country/site-specific differences evaluated during this world-monitoring study.	We thank the reviewer for the detailed review and comments. In response to the suggestion to add in some country/site-specific differences to the conclusion, we have made the following revisions, which we hope will be suitable to the reviewer: - Results (3rd paragraph) – added text specific to presence of gastrointestinal manifestations and comparisons by site/country - Discussion (4th paragraph) – to add the text ‘ with similar findings across sites’ related to the proportion of patients with presence of villous atrophy at last follow-up visit - Discussion (last paragraph) – following underlined text was added to provide additional clarity “Overall, the monitoring of patients, including the rate of follow-up biopsy, varied across the participating sites, <u>with a higher proportion of Norwegian patients receiving a follow-up biopsy compared with patients in the</u>

			UK and US. Differences were also observed in the presentation of extraintestinal manifestations at diagnosis across the sites. In addition, the study results indicate that a large proportion of patients continue to have villous atrophy and continue to experience symptoms after diagnosis; a finding that was consistent across sites.'

Reviewer 2

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept – general priority
Specific Comments to Authors: In this retrospective cohort study the Authors aimed to understand different patterns of follow-up and managment for celiac disease (CD) patients from three gastroenterology celiac disease referral centres from different countries (United Kingdom (UK), United States (US), and Norway). They want to characterize patient outcomes after CD diagnosis, as the persistence of gastrointestinal and extraintestinal symptoms and villous atrophy after diagnosis. Multicentric design and the high number of patients enrolled , are strengths of the study. The authors have revised the manuscript according to comments in the peer review report. Diagnostic criteria, serological (autoantibody profile) and histological are clarified in the methods section. The authors have specified the diagnostic criteria in the discussion section, as well as they have improved metabolic data and underlined the role of metabolic disorders in CD patients in the discussion section. The authors have clarified the criteria of elegibility of patients enrolled (biopsy-confirmed celiac disease, diagnosed between 2008-2012, with at least one follow-up visit) ,which are the same for all the centres from different countries . Moreover standard parameters as celiac serologies, symptoms, gluten free diet adherence and nutritional values are the same for all sites . The only difference among countries is in follow up endoscopy/biopsy and it is noted as a limitation in the discussion section. Data on densiometry have been added to results section and avaiable serology test results at diagnosis and follow-up are added in a supplemental table and referenced in the results section. Details on last recorded follow-up with the patient , has been added to the results section. The questions raised by the reviewers have been satisfactorily answered , improving the quality of the study and bringing to more interesting results. . This study is of good quality and the results are interesting. The manuscript is appropriate for publication in the World Journal of Gastroenterology .

1	General	As indicated above	We thank the reviewer for the thorough review and feedback, and are pleased that the reviewer is satisfied with the initial responses to reviewer comments to enhancing the manuscript. No revisions were required based on this reviewer’s comments.