Response to Reviewers

Reviewer #1

Authors' response: No specific points were raised. Thank you for the positive comments, support and enthusiasm for the study.

Reviewer #2

We are thankful for the reviewer's positive comments and the criticisms raised that have increased the level of the manuscript and we address below and in the highlighted revised version of the manuscript.

Comments: "*The topic is very important as no-biopsy approach is a hot topic in adults and is clinical practise already eg. in Finland (Celiac Disease. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Gastroententerology Society. Helsinki: The Finnish Medical Society Duodecim, 2018; Fuchs et al. Aliment Pharmacol Ther "Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities". 2019) and there is also large studies from uk supporting that high serology titers alone are sufficient for CD diagnosis without biopsy (Penny et al. Gut 2021 "Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts"). There has though been concern if something significant would be missed without endoscopy as the authors elaborate also.***"***

Response: We agree with the reviewer that a non-biopsy celiac disease diagnosis is possible, and that several studies based on serology performance have investigated such an approach. This study aims to expand our knowledge on this topic (which we previously investigated in a prospective study *Ref #8* and that of *Perry et al.*), and specifically responds to a concern that arises as a result of such new diagnostic strategy, the possibility of missing upper GI concomitant morbidity. We have now added a sentence and references in Discussion in support of this notion.

Comment: "*1. References 6 and 7 are missing from the reference list. Above are few good choice*s."

Response: Thank you for this observation, references #7 and 8 have now been added including that of Perry et. al.

Comment: "3. *The authors state that Ced and alarm symptoms lowered the risk of endoscopic lesions, this means other than the lesions caused by celiac disease in duodenum I presume? And you say that the risk was reduced when the patient had alarm symptoms? How is this possible*?"

Response: The reviewer is correct about the lower prevalence of upper GI mucosal lesions that are not caused by CeD. The reviewer also inquires about patients who exhibit warning symptoms and have lower prevalence of significant upper GI mucosal damage. We believe this finding is critical, and may be explained by: a- the fact that presence of so-called "alarm symptoms" (anemia, weight loss, etc.) in classical CeD patients with GI symptoms is prevalent; b- that enrolled patients undergoing endoscopy and duodenal biopsy were symptomatic and had a **positive specific serology**; and c- that our findings were limited to the upper GI tract, and that the lower GI tract was not explored (interestingly, prevalence of colon malignancies is low in CeD patients). This has ben added to the Discusion.

Comment: "*4. The discussion should contain a chapter on the no-biopsy approach in addition to the short commentary in the last chapter. If antibody titers are high and celiac symptoms resolve on GFD, why do we need gastrointestinal endoscopy in celiac disease diagnostics in high titer patients? There doesnt seem to be any other significant lesions other than CeD as is nicely shown here."*

Response: As suggested by the reviewer, an additional statement about the non-biopsy strategy has been added to the discussion.

The new text added in lines 338-341is: Overall, the current findings, as well as those from previous studies, support the notion that a non-biopsy approach could be implemented for the diagnosis of CeD in adult patients who meet recommended and strict serological criteria.

Comment: "*5. Reflux: H.pylori esophagitis, the need for gastric biopsies and gastric ulcers is now discussed in several different chapters though they are somewhat the same thing*"

Response: Our study only explored the prevalence of upper GI mucosal concomitant morbidities in this multicenter and multinational report. The reviewer is correct in that upper endoscopy can be helpful for patients with symptoms of esophagitis (which is a frequent clinical finding in CeD patients not doing well on a GFD) or to explore the *H. pylori* status in cases requiring persistent treatment with PPI. However, this does not seem to be supported by the risk of severe complications in the long-term of CeD patients. This is now addressed in the revised manuscript.

Reviewer #3

Thank you for the positive comments. As suggested English was revised by one of authors (EFV)