

Manuscript ID: 81168

Manuscript Title: Celiac disease screening in patients with cryptogenic cirrhosis

Name of Journal: World Journal of Gastroenterology

Date of Sending for Revision: 2022-11-26

Deadline for Revision: 2022-12-10

Response to Reviewer's Comments:

We would like to thank you for providing invaluable advices regarding our LETTER TO THE EDITOR. We hope we will be able to address your comments properly.

REVIEWER: 1

This is a letter related to the article by Singh et al. and discussing the link between celiac disease and cirrhosis. The authors properly quoted studies demonstrating that celiac disease can be a cause of cryptogenic cirrhosis and the effect of gluten-free diet (GFD) treatment in cirrhosis. For the above mentioned reasons, they recommend to detect and treat celiac disease in individual with cryptogenic cirrhosis. The letter raises an important issue and is of clinical relevance.

However, to further improve the commentary, there are two adjunctive topics worth mentioning and supporting a link between celiac disease and cryptogenic cirrhosis:

1) it is well-known that celiac disease patients may not rarely present cryptogenic hypertransaminasemia as previously demonstrated (Anti tissue transglutaminase antibodies as predictors of silent coeliac disease in patients with hypertransaminasaemia of unknown origin. Dig Liver Dis. 2001 Jun-Jul;33(5):420-5), and this might explain why some celiac unrecognized celiac patients may develop cirrhosis.

A: *We have added this information and this reference to the LETTER.*

2) from the pathogenetic point of view, it has been previously demonstrated that celiac disease patients may develop autoantibodies to filamentous actin (anti F-actin antibodies) that are historically associated to type 1 autoimmune hepatitis, as previously reported (Anti-actin IgA antibodies in severe coeliac disease. Clin Exp Immunol. 2004 Aug;137(2):386-92; Antibodies to filamentous actin (F-actin) in type 1 autoimmune hepatitis. J Clin Pathol. 2006 Mar;59(3):280-4). This could further support an immunological link between celiac disease and liver injury eventually leading to cirrhosis.

A: *We have added these references and this information to the LETTER.*

REVIEWER: 2

Here are my comments regarding the letter to the editor by Schiavon entitled "Celiac disease screening in patients with cryptogenic cirrhosis": - The authors want to emphasize in this letter that patients with cirrhosis should also be tested for celiac disease. In the paper by Singh et al. they state that there is low amount of reliable evidence of testing celiac disease but say that it could be worthwhile. I believe the authors of the guidelines and this letter are in somewhat in agreement so I believe the message of the letter should be brought up better. I believe the main message is that although data is scarce as brought up by Singh et al., the result of cirrhosis can be fatal and thus all cirrhosis patients should be tested for celiac disease. If this is the message it should be brought up stronger.

A: *We have added this information to the LETTER.*

- It should also be brought up that many other guidelines have more firm guidance on testing all patients with unclear elevation in liver enzymes and in cirrhosis. See European guidelines by EssCd and ESPGHAN (Al-Toma et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders; Husby et al. European

Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2019)

A: *We have added this information to the LETTER.*