

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 60647

**Title:** Serum 1,3-Beta-D-Glucan as a noninvasive test to predict histologic activity in patients with inflammatory bowel disease

**Reviewer's code:** 03713791

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Associate Professor, Doctor, Research Fellow

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Brazil

**Manuscript submission date:** 2020-11-11

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-12-23 17:12

**Reviewer performed review:** 2020-12-26 15:02

**Review time:** 2 Days and 21 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

In the present prospective study Farias et al investigated serum levels of 1, 3 beta-D-glucan (BG) in patients with inflammatory bowel disease (IBD) and found that BG correlated with clinical, endoscopic and laboratory investigations suggestive of active inflammation. Additionally, improvement of IBD disease activity paralleled with declining BG levels. Main comments: 1) My most relevant point concerns the fact that BG is a component of bacterial cell wall. Therefore, were conditions that may interfere with correct BG estimation (SIBO, Salmonella, Shigella infection) ruled out in IBD group? 2) Do not report interquartile range in square brackets (it seems to be a reference list). 3) It would have been interesting to calculate r correlation with scatterplots between BG, FC and CRP. 4) Table 3: you can not compare by a statistical test disease location of UC and CD, these data are not comparable. 5) Sample size calculation is absent. 6) Please report the cut-off for BG that was used for ROC analysis. 7) Demographic characteristics of the whole control group should be reported in a table and compared with the IBD group. 8) Authors affirmed that, in control group, some patients with diverticular disease were enrolled. What about the BG levels in this subgroup of patients compared to IBD? Indeed, FC may be high in diverticulosis, and if this phenomenon does not occur for BG, it could be very handfull for clinical practice.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 60647

**Title:** Serum 1,3-Beta-D-Glucan as a noninvasive test to predict histologic activity in patients with inflammatory bowel disease

**Reviewer's code:** 03474080

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Associate Professor, Chairman

**Reviewer's Country/Territory:** Turkey

**Author's Country/Territory:** Brazil

**Manuscript submission date:** 2020-11-11

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-12-27 17:08

**Reviewer performed review:** 2020-12-27 17:14

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

It was novel and well presented study. I have no additional recommendation.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 60647

**Title:** Serum 1,3-Beta-D-Glucan as a noninvasive test to predict histologic activity in patients with inflammatory bowel disease

**Reviewer's code:** 03478404

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Romania

**Author's Country/Territory:** Brazil

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**Reviewer chosen by:** Ya-Juan Ma

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

This study is among the very few researches that addressed the correlation of BG with clinical, endoscopic and histological activity, as well as with some serological biomarkers and fecal calprotectin. The manuscript is original and represents a novelty, which, if replicated in other studies could represent a non-invasive test that could help monitoring IBD patients under different therapies. Very good impact on our practice and a cost-effective method! However, some points should be addressed/ clarified by the authors.

1. ABSTRACT: Methods: a. Please mention where and also the period the study was carried out. b. Biomarkers should mention also IL-17 and IFN-gamma (since they appear in the Results). Results: a. The sentence “Compared with endoscopic (AUC: 0.656;  $p=0.001$ ) and histologic (AUC: 0.853;  $p<0.001$ ) healing, no significant correlation was found between serum BG and transmural healing based on MRE (AUC: 0.576;  $p=0.192$ )” refers to CD I suppose. Since it mentions transmural healing! Then please clarify. Where is this in the main text? b. The sentence: “Performance analysis showed that the BG results were remarkably better for predicting histologic inflammation than FC and CRP”: Please mention the levels and correlations. c. Also, the cut-off values for histological remission should be mentioned. In fact, this is the title of the manuscript. Conclusion: Should include histological remission (according to the title). Or, the title to be changed to “Serum 1,3-Beta-D-Glucan as a Noninvasive Test to Predict Histologic ACTIVITY in Patients with Inflammatory Bowel Disease” This would also be in accordance with the hypothesis of the study, as the authors wrote: “We hypothesized that the serum levels of BG could reflect ACTIVE intestinal inflammation”. Please decide and write accordingly.

2. INTRODUCTION: a. Please add after references 3 and 4, the following references: 1. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Gearry R, Krishnareddy S, Lakatos PL,

Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol*. 2015 Sep;110(9):1324-38. doi: 10.1038/ajg.2015.233. Epub 2015 Aug 25. PMID: 26303131. 2. Darr U, Khan N. Treat to Target in Inflammatory Bowel Disease: An Updated Review of Literature. *Curr Treat Options Gastroenterol*. 2017 Mar;15(1):116-125. doi: 10.1007/s11938-017-0130-6. PMID: 28161818. 3. Agrawal M, Colombel JF. Treat-to-Target in Inflammatory Bowel Diseases, What Is the Target and How Do We Treat? *Gastrointest Endosc Clin N Am*. 2019 Jul;29(3):421-436. doi: 10.1016/j.giec.2019.02.004. PMID: 31078245. 4. Colombel JF, D'haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. *J Crohns Colitis*. 2020 Feb 10;14(2):254-266. doi: 10.1093/ecco-jcc/jjz131. PMID: 31403666. b. The aim stated: "...to establish an optimal cut-off level of BG to predict mucosal healing". Please then present the optimal cut-off level that predicts MH also in the abstract. 3. MATERIAL AND METHODS: a. Study population: 1) Please mention whether patients under proton pump inhibitors previously were excluded as well (important, as they modify GI microbiota, levels of fecal calprotectin as well etc). What about those receiving probiotics prebiotics or synbiotics? They modify GI microbiota, as this is the reason they are used! Same for the control group (previous medication)! If not, this could introduce an important bias! 2) The number of patients with CD and UC should be mentioned here, as it is presented in the Abstract. Only the number of people in the control group is mentioned. 3) One note here: Patients with IBS are also known to experience intestinal dysbiosis and it could influence the BG levels. It would have been better to include only healthy controls. This should be mentioned as a limit of the study. Another important bias!

b. Assessment of disease activity: 1) For SES-CD and respectively Mayo endoscopic subscore the original references should be used, instead of some papers that cited them (to replace the present 36, 37 and 38): for SES-CD: Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc.* 2004 Oct;60(4):505-12. For MES: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625-9. 2) Regarding the criteria for the presence of inflammatory activity at MRE, parietal thickness of > 3 was not included and this was the most universally accepted parameter (as mentioned in many papers - one example - Maconi G, Armuzzi A. Beyond remission and mucosal healing in Crohn's disease. Exploring the deep with cross sectional imaging. *Dig Liver Dis* 2017; 49: 457-458 [PMID: 28449813 DOI: 10.1016/j.dld.2017.04.009]. Besides, wall thickness is included in most-used magnetic resonance scoring systems: MaRIA, London, Nancy and Clermont. 3) The authors wrote: "Patients with IBD were selected consecutively depending on the presence of active disease based on both clinical and endoscopic evaluation." Why not histologic activity as well? Since it was presented. 4) Another aspect that should be further discussed is that the population of patients with IBD is very heterogenous, including various therapies. **RESULTS:** a. In the sentence, "One hundred fifteen patients with CD (sixteen with ileal [L1], thirty-nine with colonic [L2], and sixty with ileocolonic [L3] CD, and fifty-one patients with UC), fourteen", please insert the parenthesis before "Fifty-one patients with UC", as they do not have CD. b. It appears that not all patients underwent ileocolonoscopy, as in the sentence about histology, ileocolonoscopy is mentioned in only 71 in CD and 29 in UC) - "Histological activity was detected in 33 of 71 (46.5%) patients with CD and 9 of 29 (31%) patients with UC WHO UNDERWENT ILEOCOLONOSCOPIES". Or, the histological activity was not





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measured in all patients that underwent ilocolonoscopies? Please correct/clarify if this is just the result of the translation. c. Why did the authors choose to analyse BG in both UC and CD together and not in each disease? (Figure 3) d. Same for Table 2. It would be crucial to know cut-off, sensitivity, specificity, PPV, NPV and accuracy separately in UC and CD. I suggest to present also a separate analysis. OTHER COMMENTS: There are no Conflict-of-Interest Disclosure Form and Copyright License Agreement. Please insert.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

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**Academic degree:** MD

**Professional title:** Associate Professor, Doctor, Research Fellow

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Brazil

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**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Answers were satisfactory, the paper may be accepted.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Gastroenterology

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**Title:** Serum 1,3-Beta-D-Glucan as a noninvasive test to predict histologic activity in patients with inflammatory bowel disease

**Reviewer's code:** 03478404

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Romania

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<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS



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I am very pleased after reading attentively the new version of this manuscript. I highly appreciate that the authors performed the corrections and considered my comments, as well as those of the other reviewer. All these involved a lot of work, but it was really worth it. It is also very important that they changed the title of the manuscript, according to my suggestions. It makes more sense now. To summarize, all additions were performed, changes were made in all sections of the article and new figures were added. The manuscript is excellent now, appearing very professional and clear. Congratulations! Also, the missing files (Conflict-of-Interest Disclosure Form and Copyright License Agreement) were added. I strongly support the publication of this original research.