

September 10, 2018

Professor Xue-Jiao Wang, MD  
Science Editor  
Editorial Office 'World Journal of Gastroenterology'

RE: 40814

Title: Practical fecal calprotectin cut-off value for Japanese patients with  
ulcerative colitis

Dear Professor Xue-Jiao Wang:

Thank you for your e-mail of August 27, 2018 with regards to the  
above-mentioned manuscript. We also appreciate valuable suggestions of the  
reviewers.

Based on your kind comment, we have made an extensive re-write of the text of  
the paper. We believe we have adequately responded to the comments.  
Attached please find a completely revised manuscript and a response to the  
issues raised by the reviewers.

Your kind consideration of this revision for publication in WORLD JOURNAL  
OF GASTROENTEROLOGY would be greatly appreciated.

Sincerely,

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**To the editor:**

1. Please add postcode

**REPLY:** The postcode has been added (Page 1, line 18).

2. Please submit Audio Core Tip.

**REPLY:** We have submitted an audio file describing our final core tip.

3. Please provide all authors abbreviation names and manuscript title here. The abbreviation names should be the same as the copyright. World J Gastroenterol 2018; In press.

**REPLY:** Abbreviations and names of all authors together with manuscript title have been added (Page 4, lines 15-17).

4. Please write Article Highlights.

**REPLY:** Article Highlights have been added (Page 14, lines 1-31, Page 15, lines 1-3).

Thank you for taking time to review our paper.

**To Reviewer 1:**

1. How did you select that 50 patients who underwent colonoscopy? What was the reason?

**REPLY:** Thank you for your comment. Because this study was a retrospective one, the indications for colonoscopy are not uniform. The indication for colonoscopy was clinically active disease or exacerbation of clinical symptoms in 14 subjects, assessment of therapeutic efficacy in 12 subjects, and surveillance for colorectal cancer in 24 subjects.

The retrospective nature and the heterogeneity in the indication for colonoscopy have been stated (Page 7, paragraph 5, lines 24-28). The indications for colonoscopy have been added (Page 9, paragraph 5, lines 27-31).

2. The reference for all of the scoring systems should be given.

**REPLY:** Thank you for your comment. In accordance with your comment, references for scoring systems have been added in the text of the paper and in

the reference list (Page 7, paragraph 2, line 6, page 7, paragraph 6, 31, page 18, ref.no 21,22,23).

3. What is the meaning of segmental colitis in patients with UC? This is either partially treated, CD or undetermined colitis and probably should have been excluded.

**REPLY:** Thank you for your question. Segmental colitis refers to UC of rectal sparing type, and it is distinct from Crohn's disease and indeterminate colitis. This has been briefly stated with a reference in materials and methods (Page6, paragraph 3, lines 29-31, page 7, paragraph 1, line1, page18, ref.no 20).

4. Theoretically relation between albumin and FC should have been reverse.

**REPLY:** Thank you for your comment. The level of FC was correlated with the levels of serum albumin ( $r=-0.447$ ,  $P<0.001$ ). Accordingly, there was a reverse correlation between FC value and serum albumin value.

5. In table 3 CRP is higher in non-relapsed. Very unlikely.

**REPLY:** Thank you for your comment. Because there was only a little difference in CRP value between relapsed and non-relapsed patients, we think the result was a consequence by chance.

6. Although the concept of deep (histologic) mucosal healing is well accepted in CD but the evidence in UC is not that strong. The difference should be mentioned.

**REPLY:** Thank you for your comment. We agree with the comment that histology has not been suggested as a target for the treatment of UC. In the treat-to-target concept for the management of UC, either histology or FC has not been suggested as a target. However, our observation strongly suggests that FC may be an alternative for histology.

This has been stated in the discussion (Page 12, paragraph1, lines 6-11).

Thank you for taking time to review our paper.

**To Reviewer 2:**

1. In figures 2 A, B, C the specificity is always less than 40% (the horizontal axis). Why in the text the authors reported specificity 62% (Fig 2A), 70% in fig 2B, 71% in fig 2C?

**REPLY:** In figures 1 (previous Figure 2), the horizontal axis represents "1-specificity". Thus, there is not any discordance between the text and the figure as to the specificities.

2. What explanation is given of higher cut-off values than other studies? And How they explain no superiority of fecal calprotectin to traditional biomarkers such as CRP in predicting remission in UC?

**REPLY:** Thank you for your comment. It has been reported that FC value measured by fluorescence enzyme immunoassay is higher than FC measured by ELISA [27]. We presume that this explains high cut-off values in our study. This has been stated in the discussion section (Page 11, paragraph 1, lines 5-12). As to the analysis of predictive value of FC, colonoscopy was not performed at the time of clinical remission. As a matter of fact, the relapse rate in our study population was considerably high. We thus speculate that we included subjects without mucosal healing who are prone to relapse. Such a bias seems to have resulted in no superiority of FC for the prediction of relapse.

This has been discussed in the discussion section (Page 12, paragraph 2, lines 17-21).

Thank you for taking time to review our paper.

**To Reviewer 3:**

1. Which were the criteria for performing endoscopy?

**REPLY:** Thank you for your comment. Because this study was a retrospective one, the indications for colonoscopy are not uniform. The indication for colonoscopy was clinically active disease or exacerbation of clinical symptoms in 14 subjects, assessment of therapeutic efficacy in 12 subjects, and surveillance for colorectal cancer in 24 subjects.

The retrospective nature and the heterogeneity in the indication for colonoscopy have been stated (Page 7, paragraph 5, lines 24-28). The indications for colonoscopy have been added (Page 9, paragraph 5, lines 27-31).

2. Results are interesting, but there is no discussion on the interaction with other inflammatory markers. A multivariate analysis of the predictive factors would be helpful, too.

**REPLY:** Thank you for your kind comment. In order to respond to your comment, we added results of multivariate analysis in this revision. A logistic regression analysis including FC, CRP, WBC, ESR and platelet counts as co-variables failed to show any variables associated with endoscopic remission. Cox proportional hazard model failed to identify any variable predictive of relapse. However, a logistic regression analysis indicated that FC was an independent factor associated with histological remission ( $P=0.005$ ). The application of logistic regression analyses and Cox proportional hazard model have been stated (Page 8, paragraph 3, lines 26-27, 31, page 9, paragraph 1, lines 1-2).

Results of multivariate analyses have been indicated (Page 10, paragraph 1, lines 5-8, paragraph 2, lines 14-16, paragraph 3, lines 25-27).

The significant association between FC and histology has been discussed (Page 11, paragraph 2, lines 17-21).

3. The rate of relapse is quite high 14% for 6 months of follow-up. Please explain.

**REPLY:** Thank you for your comment. Because we did not perform colonoscopy at the time of clinical remission, and since the relapse rate in the study population was considerably high (14%), we presume that we included subjects without mucosal healing who are prone to relapses. Such a bias seems to have resulted in no superiority of FC for the prediction of relapse. This has been discussed in the discussion section (Page 12, paragraph 2, lines 13-21).

4. In discussion section there is a phrase "Our present study showed that a MES of 0 is associated with a lower risk of relapse and colectomy than a MES of 1

[21,22]. " Please rectify.

**REPLY:** We apologize for a mistake in writing. The sentence has been changed (Page 11, paragraph 3, lines 25-27).

5. The value of  $FC=175$  can orientate towards a possible relapse, but the sensitivity and specificity are below 70%, this seems not a good test. This should be underlined in the conclusion.

**REPLY:** Thank you for your suggestion. As has been mentioned above, we discussed less value of  $FC$  for the prediction of relapse in our study population (Page 12, paragraph 2, lines 13-21). We also have added a need for further investigations for this topic. A sentence has been added in the final paragraph of the discussion (Page 13, paragraph 1, lines 4-5).

Thank you for taking time to review our paper.