March 05, 2021

RE: World Journal of Gastroenterology Manuscript review of Manuscript NO: 63894

Dear Editor-in-Chief,

We are submitting our revised manuscript entitled " ***Risk factors and prognostic value of acute severe lower gastrointestinal bleeding in Crohn's disease***" for consideration of publication in the *World Journal of Gastroenterology*.

We appreciate your kind consideration and valuable comments on our manuscript. We revised our manuscript according to the reviewer's suggestions. Our point-by-point responses to the concerns are included below. The revised sentences in the manuscript are shown as red-colored text.

We hope that this revised manuscript meets the publication standards of *World Journal of Gastroenterology*, and we look forward to hearing from you soon.

Sincerely,

Suk-Kyun Yang, M.D., Ph.D.

Department of Gastroenterology

Asan Medical Center

University of Ulsan College of Medicine

88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

E-mail: sky@amc.seoul.kr, Tel: +82-2-3010-3901, Fax: +82-2-476-0824

Point-by-Point Responses to the Reviewers' and Editorial office's comments:

We appreciate your kind consideration and valuable comments on our manuscript. We revised our manuscript according to your suggestions, and the point-by-point responses are included below. The revised sentences in the manuscript are shown as red-colored text. Our response to the Reviewers' and Editorial office's comments is as follows:

● **Reviewer #1:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is an interesting cohort study written by Jiyoung Yoon et al. This article must add the useful knowledge for the reader. Title and abstract are appropriate. I have no comment to be addressed.

Response:

We deeply appreciate your positive review of our manuscript.

● **Reviewer #2:**

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: We read with interest the submitted article about LGIB in patients with Crohn's disease. The following comments are for the authors:

1. How was the diagnosis of LGIB made?

Response:

We really appreciate your comment. The diagnosis of LGIB was made through diagnostic modalities such as ileocolonoscopy, computed tomography, angiography, bleeding scan, and surgery. We added the following sentences in the Method section and Results section of the revised manuscript to clarify this issue.

"We retrieved data on sex, date of birth, date of CD diagnosis, date of acute severe LGIB, disease location and behavior at diagnosis, smoking status at diagnosis, early use of medications including corticosteroids, thiopurines, and anti-tumor necrosis factor (TNF) agents, diagnostic modalities for identification of the bleeding site, identified bleeding site, and date of final follow-up." (revised manuscript, page 6, lines 16–17)

"The lesion found was defined as the bleeding site when it showed active bleeding or adherent blood clot[2]." (revised manuscript, page 7, lines 3–5)

"Of the 75 patients with acute severe LGIB, bleeding sites were identified in 19 (25.3%) patients through ileocolonoscopy, computed tomography, angiography, bleeding scan, and surgery. Capsule endoscopy or double-balloon enteroscopy was not used in the evaluation of acute severe LGIB. In the patients as a whole, the sites of bleeding were the jejunum in 2, the ileum in 12, and the colon in 5. Ileocolonoscopy was performed in 66 patients and revealed bleeding sites in 7 (10.6%) patients (colon, n = 5; terminal ileum, n = 2). Computed tomography was performed in 55 patients and revealed bleeding sites in 6 (10.9%) patients (jejunum, n = 2; ileum, n = 4). Mesenteric angiography was performed in 14 patients and identified bleeding sites in the ileum in 4 (28.5%) patients. Radionuclide bleeding scan was performed in 22 patients and identified bleeding sites in the ileum in 4 (18.2%) patients. Surgery was performed to control bleeding in 4 patients and revealed ileal ulcers with adherent blood clots in 2 (50%) patients." (revised manuscript, page 9, lines 5–17)

2. Why was rectal bleed excluded?

Response:

Thank you for your comment. We did not exclude patients with rectal bleeding, but excluded one patient with anal bleeding. We excluded this patient because the bleeding was not

associated with Crohn's disease, but was associated with hemorrhoids. This is in line with previous studies in which patients with anal bleeding were excluded.

3. Is it possible that the use of thiopurines is associated with mild disease and hence the less risk of LGIB. So is it more of association rather than causation. The same may apply to the use of biologic agents which is usually associated with a more advanced disease.

Response:

Thank you for your comment. Unfortunately, we did not evaluate disease activity such as Crohn's disease activity index at the time of diagnosis. However, early use of medications such as corticosteroids, thiopurines, and anti-TNF agents is commonly used as a surrogate marker of disease activity at the time of or at an early stage of CD diagnosis. In Korea, anti-TNF agents can only be used in patients with moderate or severe disease activity who are unresponsive to both corticosteroids and immunomodulators. Accordingly, patients with early use of thiopurines usually have a more severe disease at diagnosis than those without early use of thiopurines. Although early use of anti-TNF agents was not significantly associated with a lower risk of bleeding in our study, it was difficult to draw conclusions due to the very low rate of early use of anti-TNF agents.

4. What is the definition of "acute severe" LGIB?

Response:

According to the definition used in a previous study (Kim et al., *Dig Liver Dis* 2012; reference #1 in the manuscript), we defined "acute severe LGIB" as acute overt rectal bleeding that resulted in 1) an abrupt decrease in the hemoglobin level to < 9 g/dL or at least 2 g/dL below the baseline and/or 2) transfusion of at least two units of blood within 24 hours. This is mentioned in the Materials and Methods section of the manuscript. We hope this explanation suffices.

5. What is the definition of "early use" of thiopurines?

Response:

According to the definitions used in previous studies (references #7–10 in the revised manuscript), we defined "early use" of thiopurines as the initiation of therapy within 6 months of diagnosis and at least 6 months before the first intestinal resection and acute severe LGIB episode. This is mentioned in the Materials and Methods section of the manuscript. We hope this explanation suffices.

6. How are the results different from previous studies cited by the authors?

Response:

Thank you for your comment. We presented the prognostic value of a history of acute severe LGIB in the subsequent clinical course of CD, and this issue has not been addressed in any of the previous studies including those cited by us.

We also presented the strength of our study in the Discussion section as follows:

> "The strength of our present study is that we used a well-defined inception cohort, which enabled us to identify the patients' demographic and clinical characteristics at the time of or at an early stage of CD diagnosis that could predict the occurrence of acute severe LGIB."

In contrast to the results of our study, two previous studies suggested that bleeding was more common in patients with colonic involvement than in those with isolated small bowel disease. This issue is presented in the Discussion section as follows:

> "In the present study, patients with ileal disease at diagnosis had a higher risk of bleeding compared with those with colonic disease at diagnosis, although the result did not reach statistical significance. This is in line with the results of previous studies that ileal disease is a predictor of complicated behavior[25] and surgery[17,26,27], whereas colonic disease is a predictor of a milder disease course[17,28]. However, other studies reported contrasting results in that bleeding was more common in patients with colonic involvement than in those with isolated small bowel disease[2,29]. These conflicting results warrant further targeted investigation."

Thank you again for reviewing our study in detail and providing helpful comments. We hope that our responses and the corresponding revisions are satisfactory.

● **Reviewer #3:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I read the manuscript with interest. The study is very interesting. The title is appropriate. Appropriate abstract. Well written results and discussion. It is not clear how the diagnosis of bleeding was made. It is not clear what type of instrumental and / or radiological investigations were used. The authors should provide some clarification in this regard. The tables are complete and exhaustive.

Response:

We highly appreciate your comment. The diagnosis of LGIB was made through diagnostic modalities such as ileocolonoscopy, computed tomography, angiography, bleeding scan, and surgery. We added the following sentences in the Method section and Results section of the revised manuscript to clarify this issue.

> "We retrieved data on sex, date of birth, date of CD diagnosis, date of acute severe LGIB, disease location and behavior at diagnosis, smoking status at diagnosis, early use of medications including corticosteroids, thiopurines, and anti-tumor necrosis factor (TNF) agents, diagnostic modalities for identification of the bleeding site, identified bleeding site, and date of final follow-up." (revised manuscript, page 6, lines 16–17)

> "The lesion found was defined as the bleeding site when it showed active bleeding or adherent blood clot[2]." (revised manuscript, page 7, lines 3–5)

> "Of the 75 patients with acute severe LGIB, bleeding sites were identified in 19 (25.3%) patients through ileocolonoscopy, computed tomography, angiography, bleeding scan, and surgery. Capsule endoscopy or double-balloon enteroscop

y was not used in the evaluation of acute severe LGIB. In the patients as a whole, the sites of bleeding were the jejunum in 2, the ileum in 12, and the colon in 5. Ileocolonoscopy was performed in 66 patients and revealed bleedin g sites in 7 (10.6%) patients (colon, *n* = 5; terminal ileum, *n* = 2). Computed tomography was performed in 55 patients and revealed bleeding sites in 6 (1 0.9%) patients (jejunum, *n* = 2; ileum, *n* = 4). Mesenteric angiography was p erformed in 14 patients and identified bleeding sites in the ileum in 4 (28.5%) patients. Radionuclide bleeding scan was performed in 22 patients and identif ied bleeding sites in the ileum in 4 (18.2%) patients. Surgery was performed t o control bleeding in 4 patients and revealed ileal ulcers with adherent blood clots in 2 (50%) patients." (revised manuscript, page 9, lines 5–17)

● **Editorial office's comments**

1) Science editor: There are 6 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors f ail to address the critical issue of self-citation, the editing process of this manuscript will be terminated.

Response:

As per your guidance on proper self-citation, we deleted 3 self-cited references (#7, # 8, and #14), and replaced reference #14 with the following reference in the revised m anuscript.

"Yamamoto-Furusho JK, Al Harbi O, Armuzzi A, Chan W, Ponce de Leon E, Qian J, Shapina M, Toruner M, Tu CH, Ye BD, Guennec M, Sison C, Dem uth D, Fadeeva O, Khan QMR. Incidence of suboptimal response to tumor ne crosis factor antagonist therapy in inflammatory bowel disease in newly indust rialised countries: The EXPLORE study. *Dig Liver Dis* 2020; **52**: 869-877 [P MID: 32563721 DOI: 10.1016/j.dld.2020.05.031]"

Accordingly, our final version of the manuscript has a total of 36 references, 3 (8.3%) of which are self-cited references. We hope that this revision satisfies the guidelines

of the journal.