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August 23, 2017

Dear Editors,

We greatly appreciate the time that the editor and the reviewers of *World Journal of Gastroenterology* took to review our article. We hereby resubmit it in a revised manuscript “Risk factors for postoperative recurrence after primary bowel resection in patients with Crohn’s disease” to be considered for publication in *World Journal of Gastroenterology* (35183).

We greatly appreciate the reviewers’ pertinent comments and have revised our manuscript accordingly. Corrections are indicated in the revised text using red colored text and our point-by-point responses to the reviewers are listed in the attachment to this letter.

Thank you for the opportunity to resubmit our manuscript. I have done my best to correct the previous version according to the reviewers’ comments and to answer the reviewers’ question. I appreciate again for the reviewers’ pertinent comments. We look forward to your response.

Yours sincerely,

Chang Sik Yu, M.D., Ph.D.

Response to the Reviewer #1's Comments:

1. Major comments

: Inclusion of any historical perspectives with a different cohort such as Caucasian population could be of interest. The data by itself will be useful based on this positive information. Appreciate the inclusion of limitation of the study.

Response: We appreciate your comment. As reviewer's comment, we revise Discussion section about different cohort such as Caucasian population (page 11 lines 11-16, 22-24).

Korean patients with CD show higher incidence of perianal disease than Western patients. Previous study in our center, perianal fistulas occurred in 46.8% of patients. Also, the cumulative frequency of perianal fistula was 54.3% after 15 years. These results are in contrast to those of Western studies in which the cumulative frequency of perianal fistula in patients with CD attending referral centers was reported to be 13–38%. Furthermore, the presence of perianal disease was one of the predictors of postoperative recurrence, as has been suggested by previous studies in Asian population. Gao et al. also assessed risk factors for surgical recurrence and advocated perianal CD correlated with a higher clinical recurrence rate. Korean CD patients with perianal disease had a higher risk of surgical recurrence. The present study showed that patients with CD who developed perianal disease after the first resection had a high risk of surgical and clinical recurrence, indicating that these patients had a poor disease outcome after the primary operation. Similarly, despite a wide variation on reported risk of recurrence, the presence of perianal disease is thus considered to be a risk factor for postoperative recurrence in Caucasian population. The presence of perianal disease is a sign of an increased inflammatory process and this may also influence intestinal CD.

2. Minor comments

: Some typographical errors are noted. Please correct.

Response: Thank you for your suggestion. We corrected some typographical errors..

Page 15 line 27: postpoperative -> postoperative

Table 2. Handswen -> Handsewn

Table 3. assassociated -> associated

Answer to the Reviewer #2's Comments:

Comment 1. Please read it once more looking for sites you repeats yourself – there are several – probably wise to erase as much as you can, some spellings errors as well.

Response: Thank you for your suggestion. We corrected some typographical errors..

Page 15 line 27: postpoperative -> postoperative

Table 2. Handswen -> Handsewn

Table 3. asssociated -> associated

Comment 2. I wonder if you could elucidate on how many patients had perianal disease before the first surgery and what fraction of those also got perianal disease postoperative.

Response: Thank you for reviewer's comment.

Among 260 patients, 122 (46.9%) patients had perianal disease before first surgery. Of these, 42 (34.4%) patients had perianal disease after first operation (page8 lines 30-31, page9 line1).

Comment 3. The same also goes to the use of anti-TNF. Looking at the postoperative use of medication it reflects a top-up strategy. Why is that?

Response: We appreciate reviewer's comment. We revised Result section about our medical treatment policy and proportion of anti-TNF agents.

Our medical treatment policy for treating CD was based on a step-up approach, with more potent therapies added if patients became unresponsive to first-line or less toxic agents. The use of anti-TNF agents in this study was less frequent than in Western studies because of the strict Korean government health insurance reimbursement policy. In our study, only 27 (10.4%) patients treated with anti-TNF agents before first surgery, and 17 (63%) patients continued anti-TNF agents after first operation.

Comment 4. Looking at the performance of surgery – almost 50 % of the patients was operated by 2 surgeons. Experience matters – could you tell us more regarding qualifications, those surgeons with lesser operations experience did they have more risks of recurrence of surgery? Make it general!

Response: Thank you for reviewer's comment. Although there are two specialized surgeons in Crohn's disease, there was no significant difference in complication or recurrence rate because more than 95% of the surgery was performed by colorectal surgeons in our hospital.

Answer to the Reviewer #3's Comments:

Comment 1. Top-down approach may have obscured the role of thiopurines or methotrexate in preventing post-operative recurrence. As both Azathioprine or 6-MP have demonstrated a preventive role in post-operative recurrence, it is a bit surprising that only anti-TNF drugs were independently associated to less recurrence. Please, discuss.

Response: We appreciate reviewer's comment. As reviewer's comment, we revised Discussion section about immunomodulators such as azathioprine or 6-MP.

Immunomodulators such as azathioprine or 6-MP has been widely used, and several studies showed that immunomodulators could reduce rate of surgery. Previous study in our center revealed that early use of immunomodulators was independently related to the decreased surgery rate ($P = 0.01$). However, immunomodulators were generally used after first surgery, it is difficult to determine their impact on decreasing the postoperative recurrence. In present study, 85% of patients used azathioprine or 6-MP after first surgery.

Comment 2. Use of antibiotics such as metronidazole and/or second generation quinolones should be analysed and discussed

Response: As reviewer's comment, we revised Result and discussion section about use of antibiotics.

Antibiotics such as ciprofloxacin or metronidazole were administered to 163 patients (62.7%) in case of infectious complications such as intra-abdominal abscess, perianal abscess or fistula before first surgery. All the patients who underwent first surgery used antibiotics for a certain period of time.

Antibiotics have not been shown to be effective for induction and maintenance of remission for active CD. The best data for antibiotics are in the short-term treatment of perianal fistula and in combination with anti-TNF for perianal CD. Aside from these indications, antibiotics should really be used to treat the inflammatory complications of CD such as enteric fistula or abscess. The main limitations to using these agents long standing are antibiotic resistance and side effect.

3. There is some typo errors: Asan instead of Asian p.5 line 8.

Response: Thank you for your comment. We corrected some typo errors..

Page 15 line 27: postoperative -> postoperative

Table 2. Handswen -> Handsewn

Table 3. associated -> associated

Page 5 line 8 (page 7 lines 13-14 in revised manuscript): “The study protocol was approved by the institutional review board of Asan Medical Center “