Dear Editor,

Thank you for your review of our manuscript and the comments of the reviewers. Several important points were raised which we now have addressed in the revised manuscript. The following letter summarizes our efforts to respond to the concerns of the reviewers, and lists changes in the manuscript. We consider that these revisions have strengthened the manuscript significantly, and trust that it now is suitable for publication in '**World Journal of Gastroenterology**'.

If there is any further information that would be of help to you, I can be reached by e-mail at takafumiando-gi@umin.ac.jp.

Thank you again for your kind consideration of this work.

Takafumi Ando, M.D., Ph.D.

To Reviewer 1:

The biggest problem of this study is the lack of clarity on the aim of the study. As indicated in the abstract while the aim of the study was to evaluate the clinical utility of a new endoscopic score, the title introduces the concept of mucosal healing as a prediction of clinical outcome.

Thank you for this helpful comment. As you suggested, the major aim of our study was to evaluate the clinical utility of a new endoscopic score. The original title is confusing, so we would like to revise to "**Clinical utility of a new endoscopic scoring system for Crohn's Disease**" according to your suggestion. **(page 1, line 7 title)**

There is no evidence of mucosal healing (namely patients received only one assessment of their inflammatory lesions, and there is no before and after treatment study) it is incorrect to define an endoscopic score <4 as" mucosal healing".

As you suggest, a definition of mucosal healing has still not been established. In patients with a low endoscopic score, CD activity might be less than in those with a high endoscopic score. However, we could not diagnose whether mucosal healing was

obtained or not. We agree with your helpful suggestion, and have therefore defined "endoscopic score <4" as the "low disease activity group", and "endoscopic score ≥4" as the "high disease activity group". The description has been corrected in the revised version. **(page 7, line 13-14; page 8, line 1 - line 2; page 10, line 7; page 15 line 4-5)**

In addition, the description regarding the association between endoscopic score and the concept of mucosal healing has been added in the revised version. **(page 15, line3 - line 5)**

In my opinion, the study indicates that the endoscopic study of the small bowel allows a more accurate definition of the presence and degree of inflammation of the anatomical lesions. As that it could be useful in predicting the need for surgery where previous studies showed contrasting results on the utility of endoscopy for this prediction (Jauregui- Amezaga A, et al. Gut Published Online First: December 16, 2014 as 10.1136/gutjnl-2014-308101; Allez M, et al. Am J Gastroenterol 2002;97:947–53)

Thank you for your helpful comment. The utility of endoscopy for predicting intestinal surgery has not been fully established. Allez M et al. reported that severe endoscopic lesions (SELs) have a more aggressive clinical course with an increased rate of surgery, while Jauregui-Amezaga A et al. reported that the presence of SELs is not predictor of surgery in patients with CD; rather, they emphasized the importance of stenosis and/or intra-abdominal fistulae at MRI for predicting an increased risk of surgery. We agree with their discussion of the clinical importance of evaluating stenosis. To discuss the benefit of DBE more clearly, we performed additional subgroup analysis in patients without stenosis. The analysis showed a tendency to poorer surgery-free survival in patients with a high mSES-CD score (≥4) compared to low mSES-CD score, albeit without statistical significance. These results, along with previous evidence, might suggest that the evaluation of lesions other than stenosis is also potentially useful for predicting the event of surgery. Collectively, evaluation of the extent of stenosis is clearly important in predicting the risk for the event of surgery. However, the evaluation of lesions other than strictures using DBE would provide more accurate risk estimation for the event of surgery, although further validation studies are warranted. The description has been corrected in the revised version. **(page 12, line 5 – page 13, line 1)**

To substantiate their findings the AA should: ? specify if physicians who

recommended surgery were blinded or not to the endoscopic assessment and discuss the consequences ? show the total number of patients who underwent surgery and their disease's location and extension ?

As you questioned, physicians who recommended surgery were not blinded to the endoscopic assessment. Surgery-free survival is a surrogate endpoint for evaluating the clinical course of patients with CD. Because of its surrogate nature, selection bias in the assessment of endoscopy influenced the clinical decision for surgical treatment. We have added this limitation to the paper. **(page 15, line 5-9)**

The total number of patients who underwent surgery was 26 of 76 patients. Of these, the number with disease in the colorectum, both colorectum and small intestine, and small intestine was 3 (12%), 13 (50%) and 10 (38%), respectively. In accordance with your suggestion, we have shown the total number of patients who underwent surgery and their disease location and extension in the Results section of the revised version. In addition, the limitation of this issue has been added in the Discussion. **(page 10, line 10-13)**

Introduce in the graph of Figure 2, at each time point, the total number of patients at risk for surgery and the number of patients undergoing surgery .

In accordance with your suggestion, we have added the total number of patients at risk of surgery and the number of patients undergoing surgery in Figure 2. **(page 26, Figure 2)**

The Title has to be changed according to the defined major aim.

The title has been corrected in the revised version, as mentioned above. **(page 1, line7 title)**

Previous studies on endoscopy utility for predicting intestinal surgery should be discussed and contrasted with the AA results. These include also findings on Infliximab therapy and disease duration recognized in previous studies and confirmed in the present study as factors influencing surgery.

Thank you for your helpful comments. As mentioned above, the utility of endoscopy for

predicting intestinal surgery has not been fully established. Allez M et al. reported that severe endoscopic lesions (SELs) have a more aggressive clinical course with an increased rate of surgery, while Jauregui-Amezaga A et al. reported that SELs is not a predictor of surgery in patients with CD. They emphasized the importance of stenosis and/or intra-abdominal fistulae at MRI for predicting an increased risk of surgery. We agree with their discussion about the clinical importance of stenosis. To determine the benefit of DBE more clearly, we performed additional subgroup analysis in patients without stenosis. The description has been corrected in the revised version. **(page 12, line 5 – page 13, line 1)**

In addition, infliximab therapy and disease duration were significantly associated with the event of surgery. Immunosuppressants and anti-TNF therapy reduced the risk of the event of surgery, while increased disease duration significantly increased the risk of these events. Similar to their results, we found that both infliximab and disease duration were independent factors associated with surgery-free survival in this study.

The description has been corrected in the revised version. **(page 12, line21-page 13, line1)**

To Reviewer 2:

Minor revisions

A.

Introduction 1. Suggest change anti-TNF antibodies to monoclonal antibodies as newer non anti-TNF agents available.

Thank you for this helpful comment. We have changed anti-TNF antibodies to monoclonal antibodies in the revised version. **(page 5, line 10)**

2. The sentence "To date, however, a method of evaluating MH in CD which includes the small intestine has not been established" should be modified. SBCE and MRE have both been shown to be capable of assessing mucosal healing. This should be mentioned in the introduction.

Thank you for this helpful comment. The description has been corrected as follows: "To date, SBCE and MRE have both been shown to be capable of assessing mucosal healing.

However, a method of evaluating MH including the small intestinal lesion in patients with CD using DBE was not established." **(page 6, line 3-7)**

B.

Results 1. Some of the terminology is confusing. The authors should try to make reference to distance travelled proximally from ileo-caecal valve. The use of the term "oral" is unnecessarily confusing.

Thank you for this helpful comment. The term "oral" has been changed to "proximal". The descriptions have been corrected in the revised version.

2. The authors make no mention of any small bowel imaging performed prior to DBE. It would be interesting to know if (a) mucosal disease/strictures had been identified prior to DBE and (b) more proximal disease was identified.

Thank you for this helpful comment. Unfortunately, data for small bowel imaging prior to DBE were not available in this study. We plan to evaluate small bowel imaging prior to DBE in a future prospective trial.

3. Faecal calprotectin levels would be interesting if available

Thank you for this comment. Unfortunately, we did not evaluate fecal calprotectin level in this study. We agree that it would be interesting to do so, however, and will consider incorporating this variable in a future trial.

C.

Discussion 1. DBE is not always widely available. It would be nice to know where the authors feel DBE fits into the overall paradigm of CD treatment ie. Should it be performed on every patient diagnosed with CD or in selected cases.

Thank you for this helpful comment. In our retrospective cohort, 29 of 44 patients (66%) showed small intestinal lesions without abnormality in laboratory data such as CRP. We therefore consider that it is currently better to perform DBE at the initial diagnosis and evaluation of CD. When useful non-invasive biomarkers of CD are identified, the best indication of DBE in patients with CD will be established.

Major revisions A.

Results 1. The authors state that the mSES-CD is better at predicting surgery free survival compared to SES-CD. This would seem apparent as strictures tend to occur in the narrower small bowel lumen. There are a large proportion of patients (39%) in this study that had strictures at the time of DBE. Despite small numbers, a sub-group analysis of those patients without strictures would be interesting to see if (a) mSES-CD is still more predictive of surgery free survival and (b) CRP correlated more closely with mSES-CD.

Thank you for this helpful comment. In accordance with your suggestion, we performed subgroup analysis of patients without strictures. Among 27 patients, 18 showed high mSES-CD while 9 showed low mSES-CD. The low mSES-CD group tended to have better survival than the high mSES-CD group (P = 0.332, log-rank test), although without statistical significance, probably because of the small sample size. In terms of the association between mSES-CD and CRP in patients with and without strictures, a significant correlation was observed despite the small sample size (r = 0.551, P = 0.003). Collectively, these results suggests that small intestinal mucosal lesions without stricture might also be important, as well as the existence of strictures. **(page 12, line 5 - 20)**

To Reviewer 3:

The study's efforts to validate an endoscopic scoring system using newer technology is important. It is somewhat limited by its retrospective nature that only includes those patients who have been pre-selected to undergo DBE.

Abstract—Should define double balloon enteroscopy as "DBE" as is not standard definition known to all. Describe the DBE technique as all may not be familiar with this technique.

Thank you for your helpful comments. A description of the DBE method has been added in the revised paper. **(page 3, Abstract; page 6, line 22 –page 7, line 5)**

DBE was first performed in humans by Yamamoto et al. in 2000, and has been available for the clinical care of CD patients in Japan since 2003. In brief, DBE is performed using two balloons. Of these, one is attached to the tip of the endoscope, and the second is located at the distal end of an overtube. The role of these balloons is to grip the intestinal wall, thereby allowing easy further insertion of the endoscope without the

formation of redundant loops in the small intestine. (Gastrointest Endosc 2001;**2**:216-20)

At our institution we utilize transoral DBE. As such, methods describing length from ileocecal valve "on the oral side" is confusing. I would either describe length of bowel IC valve OR if from oral route length of bowel from mouth. Transanal approach and length of bowel from IC valve "on oral side" is very confusing.

Thank you for this helpful comment. The term "oral" has been changed to "proximal". The descriptions are corrected in the revised version.

Table 1—Given limitation of study that includes only those patients who were ordered DBE—should include more demographics about their disesase. E.g. disease location at diagnosis, disease behavior, duration of disease, duration of disease, presence of SB disease by wireless capsule endoscopy, by radiography e.g. MRI, CT scan fluoroscopy.

The demographics of disease location at diagnosis, disease behavior, and duration of disease have been added to the revised version. Unfortunately, we did not perform capsule endoscopy in this study population. In accordance with your suggestion, Table 1 has been amended. **(page 22, Table 1)**

Inclusion of #lesions is misleading. Recommend including # patients that have findings. Also define "lesions". As only 39/76 could have lesions identified at 80cm, there must be multiple lesions described for each patient. This is misleading. Add headings for tables and N plus percentage for better comparison.

Thank you for this helpful comment. The term "number of lesions" in Figure 1 was incorrect. "Number of patients" is the correct term. As show in the Results section (page 7, line 24 – page 8, line1), 39/76 means that 39 of 76 patients had stenosis which hampered passage of the scope to 80 cm on the proximal side of the ileocecal valve. In accordance with your suggestion, Figure 1 has been corrected. The number of patients showing the presence of small intestinal lesions per total no. of patients with success on observation in each segment is shown in Figure 1: observation by DBE was successful at 0-40 cm, 40-80 cm, 80-120 cm, 120-160 cm in 59, 35, 17, and 5 patients, respectively. For instance, 46 of 59 patients showed the presence of a small intestinal lesion in 0-40

cm. (**page 21, Figure legends page 25, Figure 1)**

SES-CD may have been less predictive b/c of your population is self-selected and likely biased toward including patients that have mainly small bowel disease.

Thank you for this reasonable comment. We did not choose any patients deliberately. We included all patients with CD who underwent transanal DBE in our hospital, which happened to include a small number of L1 patients compared to L2 and L3. We agree with your comment: if more L1 patients had been included, SES-CD might have been more predictive. We have made this point clear in the last part of the Discussion as one of the limitations of our study.