

Response to Reviewer 1

[Cover Letter]

Dear Reviewer,

We appreciate you for your precious time in reviewing our paper and providing valuable comments. It was your valuable and insightful comments that led to possible improvements in the current version. We have carefully considered the comments and tried our best to address them. We hope the manuscript after careful revisions meet your high standards. The authors welcome further constructive comments if any. Below we provide the point-by-point responses.

Sincerely,

Kai Xia

Diagnostic and Treatment Center for Refractory Diseases of Abdomen
Surgery, Shanghai Tenth People's Hospital, Shanghai, China

21 October, 2022

[**Major Comments**] This study introduces Crohn's disease from the aspects of surgical indications, serious complications, clinical factors affecting the timing of surgery, and the value of early intervention. Figure 1 is beautifully created and valuable. But, unfortunately, I can't feel the innovative value of this research. In addition, the author should explain the future research direction at the end. The author can also consider adding more pictures or tables to help sort out ideas.

Response: Thanks for your good questions. CD is a gastrointestinal tract chronic inflammatory disorder with an increasing incidence worldwide, and which has contributed to an increasing burden on healthcare systems. Medical treatment is the first line of option, while surgical intervention also plays an important role in the comprehensive treatment of CD. Inappropriate

surgical timing may cause irreversible serious consequences for CD patients. This mini-review mainly focuses on the value of surgery in the comprehensive treatment of CD and the choice of surgical timing.

At present, multi-omics researches have been applied to all aspects of disease research. Thus, in the part of conclusion, the authors believe that multi-omics researches are the general direction of future research. With the deepening of multi-omics researches such as radiomics, metabolomics and microbiome, it will provide more favorable basis for individualized timing of CD surgery and identify the early changes of CD related acute lesions.

What's more, we add Table 1 in the revised manuscript. It focuses on the relationship between drug factors and surgical complications of CD.

Response to Reviewer 2

[Cover Letter]

Dear Reviewer,

Thank you for your email to provide some valuable comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below.

Sincerely,

Kai Xia

Diagnostic and Treatment Center for Refractory Diseases of Abdomen
Surgery, Shanghai Tenth People's Hospital, Shanghai, China

21 October, 2022

[Major Comments] I would like to congratulate the authors on this extensive

review of Crohn's disease therapies. Authors are recommending early surgery but I would like more details about quality of life following surgeries in this population. I think we need some details on this aspect before universally recommending surgical therapy as first line because surgeries are not a permanent cure for CD.

Response: Thanks for your good questions. Surgical intervention plays a vital role in the comprehensive treatment of CD, especially early surgery. A clinical trial by Ponsioen et al¹ revealed that early laparoscopic surgery for localized CD could improve the overall quality of life of patients and reduce the rate of recurrence and reoperation. What's more, a prospective study evaluating the effect of surgical resection on quality of life in patients with IBD by health-related quality of life (HRQL) found that HRQL scores were low in many patients with IBD referred for operation and HRQL scores improved postoperatively to levels comparable to those of the general population². A long-term follow-up study by Stevens et al³ during the LIR! C-trial revealed that most patients with localized CD who underwent early surgery were free of anti-TNF treatment, and none required a second surgery. Conversely, almost half of the patients who underwent anti-TNF treatment moved on to a Crohn-related resection. Therefore, early surgical intervention is a reasonable option for CD patients who meet the indications for surgery.

References:

1 **Ponsioen CY**, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Bossuyt PMM, Hart A, Warusavitarne J, Buskens CJ, van Bodegraven AA, Brink MA, Consten ECJ, van Wagensveld BA, Rijk MCM, Crolla RMPH, Noomen CG, Houdijk APJ, Mallant RC, Boom M, Marsman WA, Stockmann HB, Mol B, de Groof AJ, Stokkers PC, D'Haens GR, Bemelman WA. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017; **2**:785-792. [PMID: 28838644 DOI: 10.1016/S2468-1253(17)30248-0]

2 **Thirlby RC**, Land JC, Fenster LF, Lonborg R. Effect of surgery on health-related quality of life in patients with inflammatory bowel disease: a prospective study. ARCH SURG-CHICAGO 1998; **133**:826-832. [PMID: 9711955 DOI: 10.1001/archsurg.133.8.826]

3 **Stevens TW**, Haasnoot L, D'Haens GR, Buskens C, de Groof EJ, Eshuis EJ, Gardenbroef TJ, Mol B, Stokkers PCF, Bemelman WA, Ponsioen CY. OP03 Reduced need for surgery and medical therapy after early ileocaecal resection for Crohn's disease: Long-term follow-up of the LIR!C trial. J CROHNS COLITIS 2020; **14**:S003-S004. [DOI: 10.1093/ecco-jcc/jjz203.002]

Response to Re-reviewer

[Comments] The authors carefully revised according to the suggestions. I think the article is rigorous and worthy of publication. I suggest accept it.

Response: Thanks for your good questions.