

Dear Editor,

We thank all the reviewers for their very insightful remarks. Following are our responses to each of the points raised by the reviewers as well as citations of the changes that were made to the manuscript (highlighted by "track changes").

Reviewer no. *03035491*

This a retrospective study aiming to characterize radiological and clinical factors associated with subsequent surgical intervention in Crohn's disease (CD) patients with intrabdominal fistulae. The Authors concluded that a bowel stricture is the only factor predictig an increased rate of surgery whilst radiological parameters may guide in selecting treatment options in patients with fistulizing CD.

I have the following comments: 1) Authors stated in their introduction the aim of the study was to characterize radiological features of cross sectional imaging of patients with intrabdominal penetrating CD disease, and to identify what factors were associated with subsequent surgical intervention . On the other hand, in methods, their primary outome was differently defined as the rate of abdominal resection performed within one year of imaging whereas the secondary outcome was the time to abdominal resection surgery. Authors should stuck with the same specific aims throughout the manuscript.

Authors response: We agree that the specific aims should be the same throughout different section of the manuscript. Therefore we deleted the relevant paragraph in the methods section on pages 9-10.

2) Table two is difficult to follow since the number of patients receiving or not surgery is not reported.

Authors response: We added a row on the top including the total no. of patients that received or did not receive surgery:

Total no. of patients n (%)	59 (47)	67 (53)
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3) In discussion, is not clear how many patients receiving or not anti-TNF treatment after imaging were more or less likely to receive surgery

Authors response: We added a comparison for patient who did not receive anti-TNF therapy on page 16: . In comparison of the 82 patients who did not receive anti-TNF therapy 48 (59%) underwent surgery ($p < 0.01$), (see table 2).

4) English Language needs polishing

Authors' response: Although the authors are native speakers of English, the manuscript was re-reviewed by an additional Native English speaker.

Reviewer no. *02945445*

The authors present a review of fistulizing Crohn's disease to try and determine predictive factors of subsequent surgery. I have several comments: Overall, the authors should be commended for their work in an era where information is lacking. There are many potential sources of bias and thus additional clarification or additional data is required in several areas:

1. The authors mention briefly some of the medical treatments prior to surgery. An emphasis on how these were controlled for in the analysis is required. It should also be listed in the variables collected in the results section (along with duration of medical treatment prior to scan).

Authors' response: Tables 1 and 2 state the medication therapy before and after the imaging study according to the main classes of pharmacological therapy that are known to affect the natural history of fistulae in CD (e.g. immunomodulators including thiopurines and methotrexate) and anti-TNF therapy. Since there is a very wide variability in specific pharmacological therapies including the duration for each of these therapies for each patient as well as changes in therapy throughout time, an analysis of each specific therapy and duration would be very complex and not likely informative.

2. Of the patients that were on treatment, it would be helpful to see what they were on after surgery (e.g. escalation or not - from no therapy to monotherapy or monotherapy to combination therapy).

Authors' response: The primary outcome of this study was the rate of surgery at 1-year post imaging with evidence of intra-abdominal fistula. Therefore the data collection was terminated at the time the patients underwent surgery. We agree that this data is interesting but is within the scope of a different study in which we are looking specifically into this question.

3. An improved definition of fistulizing disease is required. Was this solely based off CT scan reads? Or was clinical information used to identify these patients as well. What was done with questionable cases?

Authors' response: The definition of intra-abdominal fistulizing disease was solely based on CT or MRI scan reads. We revised the definition of fistulizing disease in the methods section on page 8:

Patients were included in the study if they were hospitalized or seen as an outpatient at the inflammatory bowel diseases (IBD) clinic, had intra-abdominal fistulizing CD, according to cross-sectional imaging (CT or MRI) available for analysis...

4. The definition of 'stricture' requires additional clarification as well. Was this 50% difference in diameter based on a CT or MR enterography? It is hard to tell for sure as so much of the bowel diameter depends on the amount of distention, and this may be unreliable.

Authors' response: We agree with the reviewer on the difficulty of assessing a stricture of the bowel by cross-sectional imaging. Nonetheless, the definition of 50% narrowing of the lumen in addition to a pre-stenotic dilatation was the best definition that we could find.

5. The number of patients is confusing. The abstract lists 132, though the discussion and multivariate analysis lists 126. Thus the abstract should be modified.

Authors' response: We thank the reviewer, the abstract was modified accordingly.

6. It would be helpful to include a % of patients not treated with IMs or TNFs (53-55%).

Authors' response: Table 1 states the % of patients that were not treated with IMs or anti-TNFs before the imaging study

7. While the authors mention there was no difference in disease duration of those that required surgery vs. not, it would be interesting to see if the duration of therapy had any impact.

Authors' response: In this study we specifically addressed the factor of disease duration before an imaging study demonstrated an intra-abdominal fistula. As stated before, the high variability of specific therapies including changes of therapies throughout time before the imaging study, causes this kind of analysis to become very difficult.

8. A definition for elevated CRP and low albumin should be given.

Authors' response: The definitions are cited in table 2 – For CRP, >5mg/dl for albumin, <35mg/dl

9. The paper would add from a description of symptoms (pain, diarrhea, UTI, pneumouria, fecaluria). As the authors state, there are a lot of variables not accounted for in this retrospective review - and these could help the reader interpret the findings. 10. The authors should include any additional treatments (percutaneous drainage, IV antibiotics) as these may have had a significant bearing (successful vs. not) on the subsequent need for surgery. It would again help the reader interpret the study better as at present, it is difficult to know how to use the information in the study (in its current form). 11. Were any data available on the decision to proceed to surgery vs. not (e.g. patient refusal despite recommended surgery, gastroenterologist or surgeon referral, etc)? 12. Enterocutaneous

fistulas should be further subdivided into high output vs. low output (see: symptoms comment) to help the reader determine how to interpret the results.

Authors' response: We certainly agree with the reviewer that clinical symptoms, additional treatments, and a specific statement on the decision for surgery would help interpret the findings (e.g. Do asymptomatic patients have a different risk for surgery). Unfortunately due to the retrospective nature of this study, as well as the fact that we did not limit the study only to hospitalized patients (as this would certainly cause a significant bias), clinical parameters were not available for all patients close to the time that the cross-sectional imaging was performed (ie some patients, especially those without significant symptoms were seen in the clinic several weeks after the imaging study was performed). The question of percutaneous drainage can be assessed indirectly, as all patients with a significant intra-abdominal abscess were drained percutaneously.

13. Table 2 is quite lengthy. Removing the age <18 data (since it is such a small number) can help. Same for imaging before or after 2010 as it did not seem to make much of a difference and is not the major focus of the paper.

Authors' response: This was done accordingly in the table, and the text of the results section was modified accordingly (page 13):

Comparison of patients who did or did not have surgery within one year of the imaging study showed that there were no differences in age at diagnosis or at the time of the imaging study (less or above 18 yrs), years since diagnosis, time-frame in which the imaging was performed (before or after 2010)...

14. Within the tables, significant p values should be highlighted (to call attention to them given the large amount of data).

Authors' response: This was edited accordingly.

15. In general, there are a large number of potential confounding variables. This should be emphasized as a limitation and the above recommendations can help control for some of these potential confounding factors.

Authors' response: This limitation was emphasized on page 18:

Clinical parameters such as symptoms (e.g. abdominal pain, pneumaturia) were also not analyzed in this study. In order to limit patient bias in the study we included hospitalized patients, as well as ambulatory patients. A significant proportion of the ambulatory patients were seen in the clinic several weeks after the imaging study was performed, and thus clinical parameters could not be assessed reliably for all patients

Reviewer no. 00183659

"Factors Associated with Surgery in Patients with Intra-Abdominal Fistulizing Crohn's Disease" The authors report on patients with CD and imaging and evidence of fistulae. The authors assess radiographic findings and correlate these with the primary outcome of undergoing surgery within a year of the imaging study. This study is of interest to the World Journal of Gastrointestinal Surgery. The study provides more insight into the use of imaging findings alone to predict surgery. Introduction - please add to the paragraph about surgical resection. the additional downside of surgery is that repeated resections and/or extensive resections can be associated with short bowel syndrome with metabolic and nutritional derangements.

Authors' response: We thank the reviewer for this important comment. The suggested addition to the paragraph was done accordingly (page 7):

Surgery has the advantage of immediate resection of the perforated segment of bowel, and excision of the fistulous tract. Nonetheless, due to high recurrence rates of disease, there is still a need for continuing biologic therapy following surgical intervention. The additional downside of surgery is that repeated resections and/or extensive resections can be associated with short bowel syndrome with metabolic and nutritional derangements.

Methods - in addition to dividing patients by time periods, an analysis of associated medical therapies or failure of regimens and association with surgery would be helpful.

Authors' response: Tables 1 and 2 state the medication therapy before and after the imaging study according to the main classes of pharmacological therapy that are known to affect the natural history of fistulae in CD (e.g. immunomodulators including thiopurines and methotrexate) and anti-TNF therapy. Since there is a very wide variability in specific pharmacological therapies including the duration for each of these therapies for each patient as well as changes in therapy throughout time, an analysis of each specific therapy and duration would be very complex and not likely informative.

Methods - relevant clinical factors are not included (in addition to medication regimen), including nutritional status, hospitalization history, sepsis, reason for surgery (which is key for understanding why surgeons are operating), previous surgery. Results - was the presence of other symptomatic fistula predictive - like vagina or enterocutaneous - in addition to enterovesical?

Authors' response: We certainly agree with the reviewer that clinical factors, and a specific statement on the decision for surgery would help interpret the findings (e.g. Do asymptomatic patients have a different risk for surgery). Unfortunately due to the

retrospective nature of this study, as well as the fact that we did not limit the study only to hospitalized patients (as this would certainly cause a significant bias), clinical parameters were not available for all patients close to the time that the cross-sectional imaging was performed (ie some patients, especially those without significant symptoms were seen in the clinic several weeks after the imaging study was performed).