

Dear Editors and Reviewers,

Thank you for your letter and we are pleased to know that our manuscript (Manuscript No. 81892, Retrospective Study) was rated as potentially acceptable for publication in the *World Journal of Gastroenterology Surgery*, subject to adequate revision. We thank the reviewers for their time and effort in reviewing the submitted version of the manuscript. All suggestions were valuable and very helpful for revising and improving our paper. We have studied the comments carefully and have made corrections where necessary, which we hope will meet with your approval. The revised parts of the manuscript are marked in red (a marked version of the revised manuscript is provided in the supplementary material). Please find below our point-by-point responses to the reviewers' comments:

Responses to the Reviewer comments:

To the reviewer #1 comments:

The aim of your study is important and useful in practice. MRI is a relatively non-invasive (despite rectal bag insertion) and recently an interesting tool to evaluate the activity of Crohn's disease particularly in study for small bowel.

Authors response: Thank you for your insightful review of our manuscript.

However, your hypothesis that CD anal fistula is always associated with rectal inflammation (proctitis) has some problems. First, If rectal inflammation combined with anal fistula can be evaluated better with sigmoidoscopy or anoscope. Second, isolated anal fistulizing CD is rare and have to be differentiated from another chronic inflammation, such as TB.

Authors response: Thank you for this constructive and important comment. In clinical practice, approximately 5% of individuals will have isolated perianal disease without any evidence of luminal inflammation [1]. Additionally, nearly 10% patients with CD have an anal fistula before presenting with gastrointestinal symptoms [2]. However, perianal fistulising Crohn's disease (PFCD) and glandular anal fistula have many similarities on conventional magnetic resonance imaging (MRI); therefore, it is difficult to differentiate these conditions in the early stages with conventional MRI. In this study, we investigated the potential value of MRI texture analysis in differentiating PFCD from glandular anal fistula.

Tuberculosis (TB) may involve any part of the gastrointestinal (GI) tract and intestinal TB (ITB) accounts for 2% of TB cases worldwide [3]. Intestinal tuberculosis with perianal fistula is very rare in clinical practice. In future studies, we will aim to investigate and compare conventional MRI and texture analysis in differentiating isolated anal fistulizing CD from intestinal tuberculosis with perianal fistula.

Third, texture analysis can be useful, but it seems to be difficult and too specific for peer readers to understand its parameters. More information is likely to be needed. If you show some clinical cases, it would be better.

Authors response: In this study, we analyzed the texture of the rectum and anal canal wall in the PFCD group and glandular anal fistula group to explore whether the texture feature parameters are valuable in identifying and differentiating these two types of lesions. However, a primary issue with regard to the texture field is the decipherer of the texture features in a context, even though they were somehow validated. We have added this limitation in the revised paper [4, 5].

References:

1. Schwartz DA, Ghazi LJ, Regueiro M, et al. Guidelines for the multidisciplinary management of Crohn's perianal fistulas: summary statement. *Inflamm Bowel Dis.* 2015;21(4):723-730.
2. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. *Inflamm Bowel Dis.* 2014;20(11):2022-2028.
3. Kentley J, Ooi JL, Potter J, et al. Intestinal tuberculosis: a diagnostic challenge. *Trop Med Int Health.* 2017;22(8):994-999.
4. Ren S, Zhao R, Zhang J, et al. Diagnostic accuracy of unenhanced CT texture analysis to differentiate mass-forming pancreatitis from pancreatic ductal adenocarcinoma. *Abdom Radiol (NY).* 2020;45(5):1524-1533.
5. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. *Radiology.* 2016;278(2):563-577.

To the reviewer #2 comments:

Nicely conducted and analyzed study. It will add value to the existing literature and in the management of complex fistulas by differentiating between Crohns and

cryptoglandular fistulas. In METHODS, its mentioned Considering the retrospective nature of the study, the need for informed consent was waived. Please specify as which authority (Ethics Committee) of else waived the need.

Author response: Thank you for highlighting this important point. We have corrected this as suggested. This study was approved by the institutional review board of the Affiliated Hospital of Nanjing University of Chinese Medicine; informed consent was waived owing to the retrospective nature of the study.

To the reviewer #3 comments:

The artificial intelligence based diagnosis methods have been gaining popularity lately. The design of the manuscript is acceptable. However there are some flaws. 1. Do we really need a method to discriminate Crohn's disease associated fistulas and simple fistulas. Crohn disease generally presents with so many different findings in different parts of the gastrointestinal canal even in some cases in mouth etc.

Authors response: In clinical practice, approximately 5% of individuals will have isolated perianal disease without any evidence of luminal inflammation [1]. Additionally, nearly 10% patients with CD have an anal fistula before presenting with gastrointestinal symptoms [2]. However, perianal fistulising Crohn's disease (PFCD) and glandular anal fistula have many similarities on conventional magnetic resonance imaging (MRI); therefore, it is difficult to differentiate these conditions in the early stages with conventional MRI. In this study, we investigated the potential value of MRI texture analysis in differentiating PFCD from glandular anal fistula.

2. Do you always perform perianal MRI examinations with a water sac? Do you think is it really necessary, because it is a difficult method for the patient. 3. Texture analysis or other AI techniques generally aims to ease the imaging method, increase patient comfort and/or increase the result reliability. Maybe this study should be designed to test the diagnostic reliability of the examinations without a water sac.

Authors response: Owing to the thin wall of the rectum and anal canal, it is difficult to delineate the ROI. In this study, filling the rectum and anal canal with water sacs was performed to increase the contrast with the surrounding tissue to reduce errors. Additionally, we have successfully implanted rectal water sacs in more than 1,000 cases with PFCD and glandular anal fistula.

4. As far as i can understand from the figure 2, ROI was drawn into the contours of the water sac. Is this correct, should not it be placed into the fistula tract? The way to draw the ROI and pplace the fistula must be clearly defined and figure must be accordingly chosen.

Authors response: The ROI was drawn into the contours of the fistula tract. Owing to the thin wall of the rectum and anal canal, it is difficult to delineate the ROI. In this study, filling the rectum and anal canal with water sacs was performed to increase the contrast with the surrounding tissue to reduce errors. Figures 2a and 2b show that the red part is the outlined ROI of the fistula tract.

References:

- 1. Schwartz DA, Ghazi LJ, Regueiro M, et al. Guidelines for the multidisciplinary management of Crohn's perianal fistulas: summary statement. Inflamm Bowel Dis. 2015;21(4):723-730.*
- 2. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. Inflamm Bowel Dis. 2014;20(11):2022-2028.*

We hope that the revised manuscript has addressed all the peer review concerns and will be considered suitable for publication. We are happy to revise the text further if deemed necessary. We look forward to your final decision.

Sincerely,

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