December 27, 2023

Dear editors and reviewers:

Thank you very much for providing us an opportunity to revise our manuscript (Manuscript NO: 88770 and Title: A T2WI-based radiomic-clinical machine learning model for predicting the differentiation of colorectal adenocarcinoma).

The comments from editors and reviewers are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. In this revision, we have addressed all the concerns in detail and made necessary changes to the article according to the valuable comments of the chief editor and the reviewer. **It is worth mentioning that due to the special review method of Reviewer 1, there are many comments in the article. Therefore, I have placed the response of Reviewer 1 in the supplementary material file. Please send my response file to Reviewer 1 so that Reviewer 1 can better understand the content of my modifications.** My responses to the comments are described as follows. We hope that our revised manuscript is now suitable for your requirement.

Thank you very much again for your consideration.
Sincerely,
Jian-hua Xu

E-mail: xjh630913@126.com

We appreciate all the editor's and reviewers' positive comments as well as the constructive suggestions as discussed below.

Reviewer #1:

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Response: Thank you very much for your recognition of our research and your valuable comments. You have really carefully reviewed our article and put forward many very important amendments. We have made point-by-point amendments and replies according to your comments. Since your comments after reviewing the manuscript are all in the comments, we will explain your amendments and replies to your comments point by point in the supplementary materials, so we have not replied in this document. I believe the editor has sent the document to you. I hope our revised content can meet your requirements. Thank you again! Best regards.

Reviewer #2:

Scientific Quality: Grade C (Good)

Novelty of This Manuscript: Grade B (Good)

Creativity or Innovation of This Manuscript: Grade B (Good)

Scientific Significance of the Conclusion in This Manuscript: Grade B (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear Authors, I have read your manuscript with interest. In the age of AI of course your approach is valid and worthy. I would ask, how you could involve your method into clinical usage/practice to help the routine work. As you described MR is a very good imaging tool for making the TNM for CRC. How could you add some more information to clinical decisions with your method? As MRI seems to be a reliable method, I think a complete TNM and other markers (not only grade, butMSI, LVI can be also assessed by MRI. I would appreciate some comments/discussions about it. I listed some questions/comments below, please answer them and correct the manuscript according to these I would rather use grade than degree for differentiation. Lines 11-13: why imperativus? Please correct for complete sentences. Histology grade is sometimes used as a three or four tiered classification, but you used the two-tiered, which is preferable since it is more reliable so I agree with it. Though, sometimes you still mention well and moderately differentiated tumors. Please follow

the two-tiered classification throughout the whole manuscript. Furthermore, there are some other factors which define grade: mucinous cancers, medullary type etc. Did you incorporate these kind of CRCs, too? We usually use CRC, CRAC is not used. CRC usually means adenocarcinoma, which is the vast majority of colorectal cancers. I do not think, that grading before surgery could help/change therapeutic decisions, since surgery is usually a must. But of course, any grading would help prognostisation. Actually TNM is a very strong prognosticator, which can be also performed with imaging techniques. Furthermore, MSI, tumor budding, LVI, PNI, molecular alterations etc are also very important prognosticators, which features are also examinable with imaging techniques…as you also mentioned. Could you please discuss about these, too? Especially about its AI-ability and of course in radiology setting, so not histological AI! Preoperative grading on biopsy material is not a routine, since tumor heterogeneity can alter biopsy grade, as you correctly mentioned. Please explain all abbreviations upon first mentioning. I did not see A,B and these letters in the Figures. Legends for figures should be comprehensive and self-explanatory, Eg. I saw a nice violin plot graph, but this was not mentioned in the legends. In lines 156-158 you wrote geometric features etc but in figure1 these are called/wrote differently. Please harmonize those… What does circumference and 0,1 mean in Table 1. Tables also need legends with proper descriptions. Please describe all methods you used well understandably. How do you explain the striking difference in performance of your various models? There were several ones with AUC around 1 in training, which proved to be much worse in the validation cohort. There are also a lot of unexplained abbreviations in table 2. Legend is needed. I would list abbreviations in an alphabetical order. There is no need for repeating the DOIs in the reference list.

1. Dear Authors, I have read your manuscript with interest. In the age of AI of course your approach is valid and worthy. I would ask, how you could involve your method into clinical usage/practice to help the routine work.

Response: Thank you for your comments. Relevant studies have shown that digestive tract tumors with different degrees of differentiation have differences in biological behavior and chemotherapy sensitivity. Therefore, understanding the differentiation level of tumors can help clinicians determine the malignant degree of tumors and choose the most reasonable treatment plan, including direct surgery or neoadjuvant therapy before surgery. Second, it can help to evaluate the possible prognosis of patients. At present, enhanced magnetic resonance imaging is a common evaluation method for colorectal cancer, so it can be well applied in clinical practice.

2. As you described MR is a very good imaging tool for making the TNM for CRC. How could you add some more information to clinical decisions with your method? As MRI seems to be a reliable method, I think a complete TNM and other markers (not only grade, but MSI, LVI can be also assessed by MRI. I would appreciate some comments/discussions about it.

Response: Thank you for your comments. What you said is very reasonable. MRI has been widely used to evaluate complete TNM and other markers, including MSI and LVI. We have carried out necessary discussion on them, and our modification is put in the second paragraph of the discussion. (MRI is widely used to identify poor prognostic factors, evaluate tumour T stage, evaluate liver metastasis and other aspects via CT, and evaluate rectal cancer according to the guidelines of the European Society of Oncologists and the National Comprehensive Cancer Network (NCCN). Therefore, MRI has become a necessary auxiliary technology in the diagnosis and treatment of colorectal cancer[22,23,24]. Especially in the partial stage of primary and recurrent rectal cancer, compared with techniques such as CT and rectal ultrasound, TNM staging can not only accurately predict several other high-risk features, including circumferential resection margins, the extramural vascular infiltration status, and tumour deposits, etc., to aid in tumour stratification[25-28]. Lin et al.'s[29] study combined radiomics features with CEA levels, and the established model showed good discrimination, with an AUC as high as 0.882, indicating that the model could accurately predict the preoperative T stage of rectal cancer in patients. A multicentre retrospective study conducted by Li et al.[30] showed that the imaging omics model (AUC=0.78) could suggest the MSI status of rectal cancer patients. However, it cannot replace genetic testing as the gold standard.)

3. I listed some questions/comments below, please answer them and correct the manuscript according to these I would rather use grade than degree for differentiation.

Response: Thank you very much for your correction. We have modified it according to your suggestions.

4. Lines 11-13: why imperativus? Please correct for complete sentences.

Response: Thank you very much for your correction. We have modified it according to your suggestions.

5. Histology grade is sometimes used as a three or four tiered classification, but you used

the two-tiered, which is preferable since it is more reliable so I agree with it. Though, sometimes you still mention well and moderately differentiated tumors. Please follow the two-tiered classification throughout the whole manuscript.

Response: Thank you very much for your correction. We have modified it according to your suggestions.

5. Furthermore, there are some other factors which define grade: mucinous cancers, medullary type etc. Did you incorporate these kind of CRCs, too?

Response: This study included mucinous adenocarcinoma. Mucinous adenocarcinoma is divided into two types based on the degree of histological structural differences: One type is the low-grade mucinous adenocarcinoma, which originates from well-differentiated to moderately differentiated adenocarcinoma and papillary carcinoma, whereas the other type is the high-grade mucinous adenocarcinoma, originated from poorly differentiated adenocarcinoma and signet ring cell carcinoma. Medullary carcinoma is not included in this study, because medullary carcinoma is rare, and patients with medullary carcinoma are not included in the included cases.

6. We usually use CRC, CRAC is not used.

Response: Thank you for your correction. We have made appropriate changes to the article.

7. We usually use CRC, CRAC is not used. CRC usually means adenocarcinoma, which is the vast majority of colorectal cancers. I do not think, that grading before surgery could help/change therapeutic decisions, since surgery is usually a must. But of course, any grading would help prognostisation. Actually TNM is a very strong prognosticator, which can be also performed with imaging techniques. Furthermore, MSI, tumor budding, LVI, PNI, molecular alterations etc are also very important prognosticators, which features are also examinable with imaging techniques…as you also mentioned. Could you please discuss about these, too? Especially about its AI-ability and of course in radiology setting, so not histological AI! Preoperative grading on biopsy material is not a routine, since tumor heterogeneity can alter biopsy grade, as you correctly mentioned.

Response: We think what you said is very reasonable. Our research does have limitations as you said. As mentioned above, we discussed MSI, TNM staging and other indicators appropriately in the second paragraph of the discussion. Thank you.

8. Please explain all abbreviations upon first mentioning. I did not see A,B and these letters in the Figures. Legends for figures should be comprehensive and self-explanatory, Eg. I saw a nice violin plot graph, but this was not mentioned in the legends.

Response: We have explained all abbreviations at the first mention. And indicateA and B in order on the picture. At the same time, the picture is explained in more detail in Figure legend.

9. In lines 156-158 you wrote geometric features etc but in figure1 these are called/wrote differently. Please harmonize those…

Response: Thank you very much for your comments. We have made appropriate modifications to figure 1 according to your requirements.

10. What does circumference and 0,1 mean in Table 1. Tables also need legends with proper descriptions. Please describe all methods you used well understandably.

Response: Thank you very much for your comments. We have made appropriate modifications to figure 1 according to your requirements.

11. Please describe all methods you used well understandably. How do you explain the striking difference in performance of your various models? There were several ones with AUC around 1 in training, which proved to be much worse in the validation cohort. There are also a lot of unexplained abbreviations in table 2. Legend is needed. I would list abbreviations in an alphabetical order. There is no need for repeating the DOIs in the reference list.

Response: As we described in the article (***A comparison of the models revealed that the MLP model performed better in the training cohort (AUC= 0.796; 95% CI=0.723-0.869) and the validation cohort (AUC=0.735; 95% CI=0.604-0.866) because the AUCs of the machine learning algorithms, including SVM, KNN, RF, etc., XG boost and light GBM, were overfitted, and the AUC of the MLP was greater than that of the LR; thus, the MLP showed the best discrimination and the best prediction stability (as shown in Figure 6 and Table 2)***), there were several AUCs around 1 in the training, but it was proved to be very bad in the validation queue, which was due to over fitting. We explained the abbreviations of Table 2 and deleted the duplicate DOI.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

1 Scientific classification: Grade C and Grade C. 2 Language classification: Grade B and Grade B. 3 Specific comments: (1) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A, B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: . (2) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published, and correctly indicate the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. (3) Please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP <0.05, bP <0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP <0.05 and dP <0.01 are used, and a third series of P values is expressed as eP <0.05 and fP <0.01. (4) Abbreviations other than special types of words such as COVID-19 and SARS-CoV-2 are not allowed in the article title, and no more than 18 words are allowed. The title cannot start with "the, a, an". (5) The "Article

Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text (and directly before the References). 4 Recommendation: Conditional acceptance.

Language Quality: Grade B (Minor language polishing)

Response: Thank you for your efforts in the peer review process, and we salute you. We have made reasonable revisions to the article according to your requirements.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/, or visit PubMed at: https://pubmed.ncbi.nlm.nih.gov/.

Response: Thank you for giving us the opportunity to publish the study in the World Journal of Gastrointestinal Oncology. We have supplemented the section "ARTICLE HIGHLIGHTS". the Reference Citation Analysis (RCA) is a very useful tool to help me find the most influential and cutting-edge research, which makes it easier for us to grasp the key points in the process of writing articles and improves the academic level of our articles. We will make full use of this system in the future. Thank you again for providing us with such a valuable system.

Once again, we sincerely thank the editors and all reviewers for their valuable feedback, which we used to improve the quality of the manuscript. If we need to make any other modifications, we are more than happy to make them. Thank you very much for your help. Looking forward to hearing from you. Best regards.