

September 28, 2020

Na Ma

Company Editor-in-Chief, Editorial Office

Baishideng Publishing Group Inc.

Dear Ms. Na Ma,

I wish to submit a revised version of an original research article for publication in *World Journal of Gastrointestinal Oncology*, titled “Highly accurate colorectal cancer prediction model based on Raman spectroscopy using patient serum.”

We would like to thank the reviewers for their useful comments. In the following, you will find a point-by-point response to the comments of each of the reviewers, editors and director.

Reviewer #1

- Major Comments; 3

1. In the abstract section, more clear information of study population and detailed brief results should be provided in the methods and in the results subsection.

- We appreciate this comment by the reviewer on an important aspect in this manuscript. We added the description about more clear information of study population and detailed brief results should be provided in the abstract section. Specifically, we added the sentence “Consequently, the diseases of 184 patients were colorectal cancer in 12, rectal neuroendocrine tumor in 2, colorectal adenoma in 68, colorectal hyperplastic polyp in 18, and others in 84. We used 1064-nm wavelength laser for excitation. The power of the laser was set to 200 mW.” in the abstract section (line 8-11 on page 4 of the revised manuscript, yellow highlight).

2. In the Introduction section, the more information of “Raman spectroscopy is useful in the diagnosis of colorectal[14]” should be described.

- We agree with this comment by the reviewer. Therefore, we added the sentence “Lin et al reported the result of analysis of the serum obtained from 38 colorectal patients and 45 volunteers by gold nanoparticle based surface-enhanced Raman spectroscopy, and diagnostic sensitivity and specificity were 97.4% and 100%[14].” in the introduction section (from line 25 on page 25 to line 2 on page 26 of the revised manuscript, yellow highlight).

3. In the methods section and in the results section, the 12 cases of patients with colorectal cancer were heterogeneous, ranged from stage I and IV. As mentioned by authors in the Discussion section, the rare cases of colorectal cancer may interfere with the conclusion of this study. In addition, the results assessed by Raman spectroscopy may be quietly different between patients with stage I and patients with stage IV. Taken together, aforementioned factors may result the bias and these results obtained from these patients may be cautious. Because number of colorectal cancer patients were less than patients with adenoma and heterogeneous populations of colorectal cancer patients were exhibited, the enrollment of more stage I colorectal cancer patients to further compare the data analysed by Raman spectroscopy with patients with colon adenoma, and patients with polyp are suggested.

- We agree this comment by the reviewer, and we also recognize the importance of this point. In this study, we show one of the possibilities of diagnosing colorectal cancer with serum and machine learning. So, we need to verify that the model presented in this study can really diagnose colorectal cancer. Also, since only two samples of rectal neuroendocrine tumors were analyzed in this study, we cannot give definitive results for neuroendocrine tumors. And, we have described them as the limitation of this study in a discussion section.

Based on the above, we added the words "There is a possibility that" in a discussion section (line 17 on page 16 of the revised manuscript, yellow highlight), the sentence "Additionally, since the sample from the patients with neuroendocrine tumor were only two, we could not give definitive results for neuroendocrine tumors in this study." In a discussion section (line 13-15 on page 18 of the revised manuscript, yellow highlight), and the sentence "In summary, we could present a model for diagnosing colorectal cancer with serum and machine learning in this study. However, the clinical usefulness of this model is still undecided," in a discussion section (line 2-4 on page 19 of the revised manuscript, yellow highlight).

Reviewer #2

- Major Comments; 2

1. Methods. The method is appropriate. In terms of the analysis for the AI and boosted tree model, the model seems to over-estimate the accuracy. How is the validation of the prediction model answered? Is there another database to ensure reproducibility of such results?

- We appreciate this valuable and important comment by the reviewer. In this study, we have shown a model that fits as closely as possible so that it can better show the clinical diagnosis that has already been obtained. We are currently in the process of verifying the clinical usefulness of this model and would like to report the results in the near future.

In this regard, we have made many amendments to the statements in this paper. It will be described in detail in " 2" below.

2. Discussion. Overall, I find the manuscript easy to understand and well very thought through. The main concern is in the validity of the AI model and the validity as described above.

- As the reviewer says, we have only shown the possibility of diagnosing colorectal cancer with serum and machine learning in this study, and have not proven its true clinical utility. In future studies, we must prove the clinical usefulness of the diagnostic model presented in this study.

Based on the above, we added the words “There is a possibility that” in a discussion section (line 17 on page 16 of the revised manuscript, yellow highlight), the sentence “Additionally, since the sample from the patients with neuroendocrine tumour were only two, we could not give definitive results for neuroendocrine tumors in this study.” In a discussion section (line 13-15 on page 18 of the revised manuscript, yellow highlight), and the sentence “In summary, we could present a model for diagnosing colorectal cancer with serum and machine learning in this study. However, the clinical usefulness of this model is still undecided,” in a discussion section (line 2-4 on page 19 of the revised manuscript, yellow highlight).

Science editor

- Major Comments; 3

1. The main concern is in the validity of the AI model and the validity as described above. Illustrations and tables are appropriate, and the biostatistical analysis of significance is appropriate. However, the rare cases of colorectal cancer may interfere with the conclusion of this study. The questions raised by the reviewers should be answered.

- We appreciate extremely useful comments by the reviewers. We agree with the reviewer's opinion, and have made the above corrections to the manuscript.

2. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

- We have uploaded the approved funding agency copy.

3. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

- We have uploaded figures as a PowerPoint file in the maximum editable format, except for the parts created by statistical analysis software that cannot be edited.

Editorial office director

- Major Comments; 2

1. I have changed the manuscript type “frontier” to “Retrospective Study”. The authors need to provide the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and informed consent.

- We agree the change of the manuscript type, and we uploaded the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and informed consent.

2. Please write the “article highlights” section at the end of the main text.

- We have added the “article highlights” section at the end of the main text (from line 13 on page 18 to line 3 on page 20 of the revised manuscript, yellow highlight).

Company editor-in-chief

- Major Comments; 1

I have reviewed the Peer-Review Report, the full text of the manuscript and the relevant ethics documents, all of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major revisions. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Before final acceptance, authors need to correct the issues raised by the editor to meet the publishing requirements.

- We would like to thank you for your enormous work involved in this paper. We agreed with the reviewer's comments and responded in good faith. We believe that the scientific level of this manuscript has been raised thanks to the comments of the reviewers. Please re-evaluate this manuscript.