

Dear Editor

World Journal of Gastrointestinal Oncology

Thank you for the opportunity to resubmit our manuscript entitled “Application of convolutional neural network-based endoscopic image in diagnosis, treatment and prognosis of esophageal cancer and high-grade dysplasia patients: a systematic review with meta-analysis of the diagnostic accuracy and individual data”

(manuscript ID: 87250-R1) consideration for publication in *World Journal of Gastrointestinal Oncology*. This is a manuscript written by Jun-qi Zhang, Jun-jie Mi, Rong Wang. First, we would like to thank the reviewers for an excellent review of our manuscript. Their insight and suggestions, in our opinion, have allowed us to develop an improved version of the manuscript. The comments raised by the reviewers have been addressed below.

We hope that we have adequately addressed all of the reviewers' comments and that the reviewers will be satisfied with our responses. We are very excited about our results and sincerely hope that the reviewers will find our revised manuscript acceptable for publication. Thank you for all of your help with this process.

Sincerely,

Jun-qi Zhang, Jun-jie Mi, Rong Wang

RESPONSE TO REVIEWERS' COMMENTS:

Reviewer(s)' Comments to Author

Reviewer 1

1. Have you considered the model of endoscope? Because I believe that there will be

differences in what can be done depending on the model, such as using Endocytoscopy, etc. What do you think?

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. In fact, we have considered the model of endoscope, it is is a very meaningful influencing factor, such as Endocytoscopy system (ECS). ECS is a novel ultra-high magnification endoscopic technique enabling high-quality *in-vivo* assessment of lesions found in the gastrointestinal tract with the use of intraprocedural stains. The esophagus is the most suitable site for ECS observation because it is amenable to vital staining. However, there is very little research on ECS, and only one statistically valuable literature can be provided, which was cited in the reference of Kumagai et al. [37], making it impossible to conduct meaningful meta-analysis. According to the reference “Abad MRA, Shimamura Y, Fujiyoshi Y, Seewald S, Inoue H. Endocytoscopy: technology and clinical application in upper gastrointestinal tract. *Transl Gastroenterol Hepatol.* 2020 Apr 5;5:28. doi: 10.21037/tgh.2019.11.”, the four uptodate generations of endocytoscopes have been developed. However, the limited availability of the ECS, which are only available in a small number of centers worldwide, serves as an issue on why ECS is less known and less utilized outside Japan. I think that perhaps ECS could revolutionize the field of *in-vivo* endoscopic GI cancer diagnosis, bringing us a step closer to the keen desire of every endoscopist, the so-called optical biopsy in the future.

2.You mention low grade dysplasia in the introduction, but did you not include it in

this study? If so, shouldn't it be included in the introduction?

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. We have deleted “low grade dysplasia” in the abstract and introduction according to the reviewer suggestion.

3.The endoscopic images of adenocarcinoma and SCC are completely different. Shouldn't they be considered separately? Also, there are some fundamental differences in pathological diagnosis between regions. What are your thoughts on this? In light of this, wouldn't it be better to consider obvious cancer and dysplasia separately?

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. Indeed, tumors of different histological types have significantly different shapes under endoscopy, and relevant studies have reported them separately. In this article, there are significant differences between static and dynamic images under endoscopy based on difference between CNN models. Additionally, considering the endoscopic morphology of the histological type, this article conducted relevant subgroup analysis during the statistical process. In the future, it may be possible to include more research and conduct detailed analysis.

4. The authors stated that CNN based on still images can be applied to a wide range of gastrointestinal diseases and endoscopic functions. If you state this, you should present references to CNNs for the detection and function of other diseases.

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. We have supplemented references ([63] Ding Z, Shi H, Zhang H, Meng L, Fan M, Han C, Zhang K, Ming F, Xie X, Liu H, Liu J, Lin R, Hou X, Gastroenterologist-Level Identification of Small-Bowel Diseases and Normal Variants by Capsule Endoscopy Using a Deep-Learning Model. *Gastroenterology* 2019; 157, 1044-1054.e5 [64] Shichijo S, Application of Convolutional Neural Networks in the Diagnosis of *Helicobacter pylori* Infection Based on Endoscopic Images. *EBioMedicine* 2017; 25, 106-111) to CNNs for the detection and function of other diseases.

5. The authors stated that “The CNN model should therefore allow WLI to have a stronger therapeutic impact in places where medical resources are limited and where only WLI technology is available”. It has been more than 20 years since the development of NBI and other methods. While I understand the authors' opinion, I do not believe that facilities that make decisions based solely on WLI are required to perform a thorough examination for esophageal cancer, nor are they facilities that use CNN. In addition, I believe that a certain level of endoscope model is required to use CNN, and it is unlikely that technologies such as NBI cannot be used. I think this sentence is unnecessary.

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. We deleted the paragraph “The CNN model should therefore allow WLI to have a stronger therapeutic impact in places where medical resources are limited and where

only WLI technology is available” and supplemented the missing information according to the reviewer suggestion.

Reviewer 2

1. How confident are you with the method used to pool the studies given the high heterogeneity?

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. The meta-analysis of deep learning or CNN may generally have high heterogeneity, which may be due to the influence factors. In this article, we integrated regarding influence factors such as experimental scale, region, pathological classification, endoscopic technology, and CNN model design included in the literature. Besides, we conducted a subgroup analysis and regression analysis, the findings demonstrated that the credibility of this article is not greatly affected after further statistical analysis.

2. Does the method take into consideration variance between studies? –

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. We have considered the variation between different studies. This study summarized the meaningful influencing factors that can be included in statistical analysis, and further subgroup analysis and regression analysis were also conducted. In addition, this study also evaluated the publication bias of the studies included in order to objectively evaluate the differences between literature.

3. The left side of the flowchart is empty - Nationality: Asia, Europe...It will be more

informative to provide the name of the country or change to Continent. –

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. We have supplemented the missing information.

4. "These data were derived from the previously studies, which have been cited." I think you meant "from previous studies".

>>Response:

We greatly appreciate the reviewer noting this problem with this manuscript. We have corrected the wrong word.

Editor' Comments to Author

**LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS
SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH**

>>Response:

We greatly appreciate the editor noting this problem with this manuscript. The English of this manuscript was initially revised by a native English-speaker engaged through the auspices of a professional proofreading service. In this submission, the English has been thoroughly checked and revised again. We now believe that the paper should meet the standards required for publication in your journal and should make our work accessible to the scientific community.