Response to reviewers of World Journal of Gastroenterology
Manuscript NO: 73711

Thank you for taking the time to review the manuscript, and many thanks to the reviewers for relevant comments and questions.
According to reviewers comment, revisions have been made. Below you will find a point-to-point answer to the comments and questions.

Reviewers' comments followed by authors reply (point-by-point):

Reviewer 1:

1. The authors discuss the role of AI in CCE and offer some interesting insight into the areas where it might be useful. An interesting point is the role of AI in differentiating hyperplastic and adenomatous polyps. I think the authors should mention the recent paper looking at the differential diagnosis of colorectal polyps by CCE (The Differential Diagnosis of Colorectal Polyps Using Colon Capsule Endoscopy Intern Med . 2021 Jun 15;60(12):1805-1812. doi: 10.2169/internalmedicine.6446-20. Epub 2021 Jan 15).

   Reply: Thank you for raising this important challenge. It would be a game changer towards a wider adoption of CCE to enable differentiation of hyperplastic and adenomatous polyps. Hence, we have included a paragraph addressing this matter. "To avoid unnecessary OC after CCE, it is essential to differentiate between hyperplastic polyps (HPs) and adenomatous polyps (APs). By applying flexible spectral imaging colour enhancement (FICE), Nakazawa *et al* differentiated HPs from APs with a sensitivity of 91.2% and specificity of 88.2% [10]. Further research is needed to detect sessile serrated lesions using AI-assisted CCE."

2. Although there is not much literature on this, I believe that the second generation CCE offers good quality images to be able to differentiate an adenoma from a hyperplastic polyp by optical diagnosis alone (perhaps with FICE as an adjunct). More research into this would be interesting and also incorporating the role of AI in differentiating polyp types to reduce the number of onward referrals for colonoscopy. Also, the identification of sessile serrated lesions by AI would be important given their premalignant potential and difficulty to identify at CCE. The authors could mention their thoughts re. SSLs and AI-assisted identification.

   Reply: We agree that differentiation of adenomas from SSL also is an important area for future research and in our opinion it seems doable with ongoing advances in AI. We have added the following to the letter:
   "Further research is needed to detect sessile serrated lesions using AI-assisted CCE."

<u>**Reviewer 2**</u>:

1. Although the contents of the letter were observed with interest, minor issues were identified. We agree that CCE can be considered as an alternative primary diagnostic procedure to optical colonoscopy (OC) during the Covid-19 pandemic. But cost is also an important part. In many Asian countries, OCs are less expensive than CCEs, so the role of CCEs is relatively reduced. Unlike in Asia, if CCE has better cost-effectiveness compared to OC in Europe, the role of CCE will be more emphasized if this part is added.

   Reply: We really appreciate this consideration. Cost-effectiveness is of uttermost importance for the adoption of CCE in different clinical and geographical settings. In the SCOTCAP the are close to break even on the costs of CCE as compared to OC. Further improvements in bowel preparation regimens and strategies for selection of the right patients for CCE as well as better compliance are expected to bring down the cost attributed to CCE. To address these issues we have included the following sentences: "The cost-effectiveness of CCE needs to be improved before wider clinical adoption is considered. Hassan *et al* found that improved compliance in the general population is mandatory to make CCE cost-effective compared to OC [7]."

We sincerely hope that our reply to the issues raised by reviewers are sufficient.

On behalf of co-authors

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