

Dear Editors of World Journal of Gastroenterology,

Many thanks for your efforts, and we are pleased that there is a chance to for us revise the manuscript. As you requested, the concerns of the reviewer and editors have been addressed in detail. Thanks again for your kindness and we hope to hear from you soon.

Kind regards

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**Reviewer 1:**

**Comment 1**

Specific Comments to Authors: Study is well done and it adds to the data on the use of AI to improve detection of adenomatous polyps. The study needs significant language corrections prior to publication.

**Authors' reply**

Many thanks for the reviewer's positive comments for our work. We appreciate the reviewer's suggestion and according to the reviewer's concern, we additionally invited a native-English speaker (from American Journal Experts, recommended by the editors) to edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability to ensure that the manuscript's language can meet standard of publication.

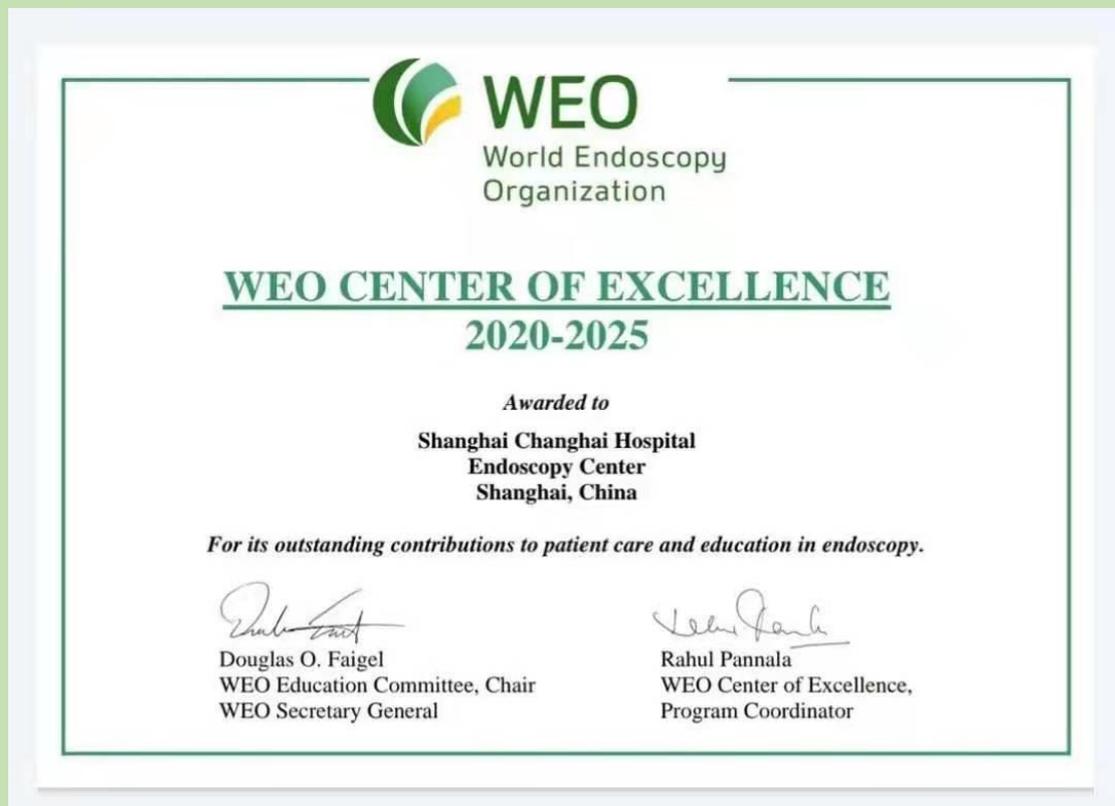
**Comment 2**

Methods: There should be comments on the polyp histology procedure, was there a central pathology reading for example?

**Authors' reply**

We appreciate the reviewer's comment and suggestion. In fact, the clinical validation was conducted in a senior endoscopy center (Changhai endoscopy center), which has been voted to be one of twenty "WEO CENTER OF EXCELLENCE" by the World Endoscopy Organization all over the world and also is one of three National Clinical Research Centers of Digestive Diseases

in China. All pathology reading and histological reports in clinical validation were carefully accomplished and checked by two experienced pathologists, which was in accordance with the guidelines of the 4th World Health Organization Classification of Tumors. For the multicenter retrospective collection of colorectal polyps, their pathological images and histological reports were rechecked by the researchers and pathologists of National Clinical Research Centers of Digestive Diseases, with unqualified images and polyps excluded.



### **Comment 3**

For Table 3 and the results of this table in the manuscript body, rather than comparing PDR among the different variables, more informative would be ADR and serrated polyp. In fact there were no serrated polyps per the supplementary tables which is somewhat unusual.

### **Authors' reply**

We appreciate the suggestion and comment of reviewer. We agree with the reviewer's opinion that ADR and serrated polyps were more informative than PDR in determining the colonoscopy quality, since adenomas and serrated polyps (mainly referring to sessile serrated adenomas/polyps) were the two most precancerous lesions for colorectal cancers<sup>[1]</sup>, and ADR is the only indicator to be consistently confirmed to be inversely associated with incidence of interval cancers<sup>[2, 3]</sup>. Generally, serrated polyps could be mainly divided into three entities: hyperplastic polyps (is considered to be less malignant), serrated sessile adenomas/polyps and traditional serrated adenomas<sup>[4]</sup>, all of which usually were not calculated as adenomatous polyps in current researches<sup>[5, 6]</sup> (they were also classified as and occupied majority of non-adenomatous polyps in our manuscript).

According to the concern of the reviewer, we rechecked the pathology report of polyps and added the comparison of sessile serrated adenomas/polyps into the Table 3 (SSR, 3.83% vs. 4.78,  $p=0.50$ ) but no traditional serrated adenomas were found in the clinical validation of the CADe due the low prevalence. In addition, since hyperplastic polyps used to be thought to be benign, we adopted an entity of clinically relevant serrated polyps<sup>[7]</sup> (defined as serrated polyps  $\geq 10$  mm and/or serrated polyps  $>5$  mm in the proximal colon,) to further validate the diagnostic performance of CADe in serrated polyps (CRSR, 9.09% vs. 11.5%,  $p=0.06$ ). Thirdly, we also compared the number of adenomas between colonoscopists and colonoscopists+CADe at different levels of subgroups, which also showed similar results that CADe also assisted colonoscopists in identifying more diminutive and flat adenomas ( $P= 0.025$  and  $P= 0.045$ , respectively) in elderly ( $\geq 50$  years, 0.43 vs. 0.46,  $P=0.045$ ) and male patients (0.38 vs. 0.41,  $P< 0.001$ ), with the aid of a new-generation colonoscope (CF-290,  $P=0.025$ ). We also added the detection of adenoma between colonoscopists

and colonoscopists+CADe as Table 4 and Supplementary table 4 into the manuscript to make a more informative result and convictive conclusion.

|                                      | <b>Colonoscopists</b> | <b>Colonoscopists+</b> | <b>P</b> |
|--------------------------------------|-----------------------|------------------------|----------|
| <b>ADR, %</b>                        | 22.0                  | 23.9                   | 0.13     |
| <b>Number of adenomas, mean (SD)</b> |                       |                        |          |
|                                      | 0.30 (0.62)           | 0.32 (0.64)            | 0.025    |
| <b>Age</b>                           |                       |                        |          |
| <50                                  | 0.14 (0.40)           | 0.15 (0.41)            | 0.32     |
| ≥50                                  | 0.43 (0.67)           | 0.46 (0.69)            | 0.045    |
| <b>Sex</b>                           |                       |                        |          |
| Male                                 | 0.38 (0.70)           | 0.41 (0.73)            | 0.045    |
| Female                               | 0.21 (0.48)           | 0.22 (0.48)            | 0.32     |
| <b>Location</b>                      |                       |                        |          |
| Proximal                             | 0.12 (0.38)           | 0.13 (0.39)            | 0.16     |
| Distal                               | 0.17 (0.46)           | 0.19 (0.47)            | 0.08     |
| <b>Size</b>                          |                       |                        |          |
| ≥10 mm                               | 0.06 (0.28)           | 0.06 (0.28)            | 1        |
| 6-9 mm                               | 0.11 (0.36)           | 0.11 (0.36)            | 1        |
| ≤5 mm                                | 0.12 (0.38)           | 0.15 (0.42)            | 0.025    |
| <b>Morphology</b>                    |                       |                        |          |
| Flat                                 | 0.20 (0.47)           | 0.21 (0.50)            | 0.045    |
| Subpedunculated                      | 0.07 (0.27)           | 0.07 (0.28)            | 0.32     |
| Pedunculated                         | 0.03 (0.21)           | 0.03 (0.21)            | 1        |
| <b>Indications</b>                   |                       |                        |          |
| Screening                            | 0.29 (0.65)           | 0.33 (0.66)            | 0.08     |
| Surveillance                         | 0.43 (0.67)           | 0.45 (0.67)            | 0.32     |
| Diagnosis                            | 0.25 (0.56)           | 0.26 (0.59)            | 0.32     |
| <b>Colonoscopes</b>                  |                       |                        |          |
| CF-Q290                              | 0.31 (0.63)           | 0.34 (0.65)            | 0.025    |
| CF-Q260                              | 0.23 (0.51)           | 0.23 (0.51)            | 1        |
| CF-Q240                              | 0.25 (0.62)           | 0.25 (0.62)            | 1        |
| <b>Experience</b>                    |                       |                        |          |
| >3000                                | 0.5 (0.72)            | 0.5 (0.72)             | 1        |
| 1000-3000                            | 0.24 (0.59)           | 0.27 (0.60)            | 0.08     |
| <1000                                | 0.23 (0.53)           | 0.26 (0.60)            | 0.16     |
| <b>BBPS</b>                          | ()                    | ()                     |          |
| < 6                                  | 0.19 (0.46)           | 0.19 (0.46)            | 1        |
| ≥ 6                                  | 0.32 (0.64)           | 0.35 (0.66)            | 0.025    |
| <b>Withdrawal time</b>               | ()                    | ()                     |          |
| < 6 min                              | 0.22 (0.57)           | 0.22 (0.60)            | 0.32     |
| ≥ 6 min                              | 0.38 (0.65)           | 0.42 (0.65)            | 0.045    |

Notably, since the clinical validation was set to preliminarily explore the diagnostic performance, feasibility and endoscopists' acceptance of the new-established CADe in real-world colonoscopy practice, we conducted an observational study with a limited sample size for a stepwise exploration. As a result, the clinical validation could not identify statistical significance in ADR, sessile serrated adenoma/polyp detection rate (SSR), clinical serrated polyp detection rate (CRSR), which we have added it as one of the limitations of study. To further address these issues, a multicenter randomized controlled trial (NCT03967756) is being conducted to demonstrate the effect of CADe on ADR, SSR and CRSR.

#### **Comment 4**

Supplementary video 1: Even though this is a supplementary video, the demarcation of one polyp is good enough as an example, four is repetitive

#### **Authors' reply**

We appreciate the reviewer's suggestion and according to reviewer's concern, we shortened the length of Supplementary video 1 to only show the process of labeling the first polyp.

#### **Comment 5**

Figure 2 is not necessary; Supplementary tables 3, 6 and 7 are not necessary

#### **Authors' reply**

We appreciate the reviewer's suggestion and deleted the unnecessary Figure 2 and Supplementary tables 3. We agree with the opinion that original Supplementary tables 6 and 7 were too heavy and unnecessary, but they might provide a part of key information about the baseline characteristics

and CADE's diagnostic performance for colonoscopy videos. Therefore, we deleted the original Supplementary tables 6 and 7 and re-organized the data to build new Supplementary tables 5 and 6 for a more concise manuscript. We hope that the revision could provide more key information for readers but would not bring more unnecessary details for the paper. Otherwise, Supplementary tables 5 and 6 also could be deleted in the final version of manuscript.

#### **Comment 6**

Results: "CADE identified all the 86 polyps with an overall sensitivity of 92.2% [91.9%-92.4%] and overall specificity of 93.6% [93.6%-93.7%] in terms of frame-based analysis, but showed suboptimal sensitivity for "challenging" polyps" This sentence is not worded correctly and therefore confusing. Perhaps something along the lines of Although CADE identified all 86 polyps, in terms of frame-based analysis there was an overall sensitivity of 92.2% and ... Also, if there was suboptimal sensitivity for challenging polyps what was the sensitivity and specificity for these polyps?

#### **Authors' reply**

Many tanks for the suggestion of the reviewer and according to the suggestion, we have corrected the sentence to be "Although CADE identified all 86 polyps, regarding frame-based analysis, there was an overall sensitivity of 92.2% and specificity of 93.6% for overall polyps and a sensitivity of 66.2% and specificity of 97.9% for "challenging" polyps (Supplementary table 6, Supplementary video 2).", which also provided the data of sensitivity and specificity for these "challenging" polyps.

|                 | <b>PPV, %</b>   | <b>Sensitivity, %</b> | <b>NPV, %</b>   | <b>specificity, %</b> |
|-----------------|-----------------|-----------------------|-----------------|-----------------------|
| <b>Video 7</b>  | 93.1[90.9-94.7] | 73.5[70.6-76.3]       | 97.5[96.6-97.3] | 99.4[99.2-99.5]       |
| <b>Video 8</b>  | 96.5[95.9-97.0] | 72.9[71.8-74.0]       | 86.2[85.6-86.8] | 98.5[98.2-98.7]       |
| <b>Video 10</b> | 47.0[42.2-51.9] | 77.7[72.0-82.5]       | 99.4[99.2-99.5] | 97.7[97.4-98.0]       |
| <b>Video 12</b> | 81.2[75.5-85.9] | 30.4[26.8-34.2]       | 94.6[94.4-94.8] | 99.4[99.2-99.6]       |
| <b>Video 15</b> | 53.8[45.9-58.0] | 46.9[42.9-50.8]       | 96.8[96.5-97.1] | 97.6[97.2-97.8]       |
| <b>Video 44</b> | 76.1[73.6-78.4] | 85.1[82.8-87.1]       | 98.4[98.1-98.6] | 97.2[96.8-97.5]       |
| <b>Video 47</b> | 64.0[60.7-67.1] | 40.1[37.5-42.7]       | 90.8[90.2-91.4] | 96.3[95.9-96.7]       |
| <b>Overall</b>  | 84.5[83.7-85.2] | 66.2[65.3-67.1]       | 94.5[94.3-94.7] | 97.9[97.8-98.1]       |

All videos consist of only “challenging” polyps (in the supplementary table 6 of original version) were included for calculation for sensitivity and specificity of “challenging” polyps in terms of frame-based analysis.

## **LANGUAGE QUALITY**

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript’s language will meet our direct publishing needs.

### **Authors’ reply**

We appreciate the editors’ suggestion and we additionally invited a native-English speaker (from American Journal Experts, recommended by the editors) to edit the manuscript for grammar,

sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language can meet standard of publication.

## **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 quality:** The manuscript describes a clinical and translational research of the Establishment and Validation of a computer-assisted colonic polyp localization system based on deep learning. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This study is well done and it adds to the data on the use of AI to improve detection of adenomatous polyps. The questions raised by the reviewers should be answered; (3) Format: There are 3 tables and 3 figures; (4) References: A total of 38 references are cited, including 24 references published in the last 3 years; (5) Self-cited references: There are 6 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to

editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

#### **Authors' reply**

We appreciate the editor's positive comments and suggestion. According to the suggestion of reviewer, we remove all potential improper self-citations (4 self-citations, References 9, 13, 20 and 38 in original version) and keep the most reasonable self-citations (2 self-citations, references 6 and 10 in original version) to keep the self-referencing rate less than 10% (2/34, 5.9%). Meanwhile, all questions of reviewer have been answered in the point-by-point response and no references were recommended by the reviewer.

**2 Language evaluation:** Classification: Grade C. A language editing certificate issued by MogoEdit was provided.

#### **Authors' reply**

We appreciate the editor's comment. In order to further improve the quality of language quality, we additionally invited a native-English speaker (from American Journal Experts, recommended by the editors) to edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language can meet standard of publication.

**3 Academic norms and rules:** The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and the written informed consent. No academic misconduct was found in the Bing search.

**4 Supplementary comments:** This is an unsolicited manuscript. The study was supported by National Key R&D Program of China, National Natural Science Foundation of China, etc. The topic has not previously been published in the WJG.

**Authors' reply**

We appreciate the editor's comment and uploaded the approved grant application forms or funding agency copy of all approval documents.

**5 Issues raised:**

(1) The language classification is Grade C. Please visit the following website for the professional

English language editing companies we recommend:

<https://www.wjgnet.com/bpg/gerinfo/240>;

**Authors' reply**

We appreciate the editor's suggestion and recommendation. In order to further improve the quality of language quality, we additionally invited a native-English speaker (from American Journal Experts, recommended by the editors) to edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language can meet standard of publication.

(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);

**Authors' reply**

We appreciate the editor's suggestion and uploaded the approved grant application forms or

funding agency copy of all approval documents.

(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;

**Authors' reply**

We appreciate the editor's suggestion and uploaded the original figures by PowerPoint to ensure a convenient reprocessing procedure for the editors.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

**Authors' reply**

We appreciate the editor's suggestion and added the "Article Highlights" section at the end of the main text.

**6 Recommendation:** Conditional acceptance.

**(2) Editorial office director:**

**(3) Company editor-in-chief:** 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 of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend:

<https://www.wjgnet.com/bpg/gerinfo/240>.

### **Authors' reply**

We appreciate the editor's comment and suggestion. In order to further improve the quality of language quality, we additionally invited a native-English speaker (from American Journal Experts, recommended by the editors) to edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language can meet standard of publication.

### **References**

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