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WJG manuscript number 111353 **point-by-point responses**

Dear Editor and Reviewers,

Thank you very much for your work in revising our paper titled **Artificial intelligence in inflammatory bowel disease: Current applications and future directions** submitted as a Review to *World Journal of Gastroenterology.* We are truly grateful for your valuable suggestions and insights, which have greatly contributed to enhancing the quality of our work. We have carefully addressed each of your comments and incorporated the recommended changes to strengthen the manuscript further.

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Manuscript NO: 111353

Point-by-point responses

Reviewer#1

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Excellent)

Conclusion: Minor revision

Specific comments to authors:

The manuscript entitled "Artificial Intelligence in Inflammatory Bowel Disease: Current Applications and Future Directions" is well-structured, clearly written, and presents valuable insights into the role of artificial intelligence (AI) in the diagnosis, management, and prognosis of inflammatory bowel disease (IBD). The topic is highly relevant and timely given the rapid integration of machine learning (ML) and data-driven approaches in precision medicine. However, several aspects of the manuscript require clarification and enhancement to improve its clarity, completeness, and scientific impact before it can be considered for publication following minor revisions:

1. Clarification of Novelty: The authors are encouraged to clearly highlight the novelty of their study in the abstract. While the manuscript reviews current applications, it remains unclear how this study distinguishes itself from previous reviews or systematic analyses. The authors should articulate whether their contribution lies in the scope of covered applications, the introduction of a new classification scheme, a comparative analysis of ML algorithms, or forward-looking perspectives on integration with clinical practice.

***Answer*:** Thank you for the supportive comment. Therefore, we have modified the abstract and added a materials and methods section in order to highlight the purpose of the study in different fields of IBD using Artificial Intelligence. Please see the revised manuscript

2. Clarify the Aim of the Study: The abstract and introduction should explicitly state the central aim or hypothesis of the study. Currently, the motivation and focus are somewhat diffuse. Clarifying whether the paper is intended as a comprehensive review, a critical evaluation of current ML models in IBD, or a roadmap for future directions would strengthen the reader's understanding.

   ***Answer*:** As suggested, we have introduced in the abstract the main aims of the review in the abstract and introduction, evaluating the current ML models in IBD and future perspectives in clinical trials. Please see the updated manuscript

3. Inclusion of Quantitative Data: The abstract and conclusion would benefit significantly from the inclusion of numerical data or performance metrics (e.g., accuracy, AUC, sensitivity) where applicable. These details would provide more concrete insights into the effectiveness of specific AI techniques in IBD applications.

   ***Answer*:** Thank you for the constructive comment. We have introduced in the abstract numerical data of AI techniques in the field of IBD. Please see the revised manuscript

4. Comparative Table of ML Algorithms: It is strongly recommended that the authors include at least one comprehensive table summarizing the machine learning algorithms applied to IBD research. The table should list algorithm types (e.g., Random Forest, SVM, ANN, XGBoost), their application area (e.g., diagnosis, disease activity prediction), dataset characteristics, and reported performance metrics. Such a comparison will guide readers in identifying the most effective models and highlight trends in the field.

   ***Answer*:** Thank you for your insightful and supportive comment. We introduced a table 4 in the section CURRENT CHALLENGES AND FUTURE PERSPECTIVES in order to summarize the Machine learning algorithms in IBD. Please see the revised manuscript

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Reviewer#2

Scientific Quality: Grade C (Good)

Language Quality: Grade C (Good)

Conclusion: Major revision

Specific comments to authors:

1. The abstract effectively summarizes the paper's scope and key findings. Consider adding a sentence about the practical implications or direct clinical benefits highlighted in the review, beyond just the potential.

***Answer*:** Thank you for the supportive comment. Therefore, we have modified the abstract. Please see the updated manuscript.

2. The introduction provides a good overview of IBD and the challenges in its diagnosis and management. It effectively sets the stage for AI's role. Perhaps briefly touch upon the historical context of AI in medicine or gastroenterology, before delving into IBD, to give a broader perspective.
   ***Answer*:** As suggested, we have introduced in the introduction information regarding the history of AI in Gastroenterology. Please see the revised manuscript.
3. Specific Examples and Data: The section provides good examples of AI models and their performance (e.g., Yao et al. CAD system accuracy of 83.7% , CNN-based model accuracy of 80.0%-93.3% , DL algorithm reducing evaluation duration to 3.2 minutes). Ensure that all data points presented are consistent and clearly referenced.
   ***Answer*:** Thank you for the comment. We have revised the information regarding the models and the performance in the text and tables.
4. Clinical Impact: While the section discusses how AI improves accuracy and reduces sampling errors, further elaboration on how these improvements directly translate to better patient outcomes or more efficient clinical workflows would be valuable.
   ***Answer*:** Thank you for the useful remark. Therefore, we have introduced in the section regarding endoscopic and histologic assessment with AI, data that supports using these systems in practice to increase the efficiency of the diagnostic and monitoring process.
5. Challenges of Traditional Histopathology: The paper clearly outlines the invasiveness, time-consuming nature, and subjectivity of traditional histopathological examination. This provides a strong rationale for AI. AI Model Specificity: The discussion of specific models like the DL algorithm for eosinophil density and CNN model for neutrophil and plasma cell quantification is good. When discussing the PHRI, it's noted that it "does not accurately discriminate between different grades of inflammatory severity and does not detect the presence of dysplastic changes". This critical limitation is well-identified. Gap in CD Research: The observation that most AI applications focus on UC, with less effort in CD histopathology, is an important point. Elaborating on why this gap exists (e.g., differences in disease presentation, data availability, research focus) could add depth.
   ***Answer*:** As suggested, we introduced data regarding the gap of the AI research in Crohn's disease in the section **AI IN HISTOPATHOLOGICAL EVALUATION OF IBD.**
6. Comparison with Non-AI Methods: While the paper mentions limitations of traditional methods, a more explicit and systematic comparison of AI-driven approaches with current standard-of-care methods (beyond just highlighting their drawbacks) could demonstrate AI's advantages more clearly.
   ***Answer*:** Thank you for the comment. Therefore, we introduced comparisons between AI-driven and standard methods in the studies regarding endoscopic and histologic assessment.
7. Limitations of AI: While some limitations are touched upon (e.g., data quality, bias, cost, ethical concerns), a dedicated subsection at the end of the "Current Challenges and Future Perspectives" could comprehensively list the current limitations of AI itself in IBD, rather than just the challenges of its implementation. This could include, for example, the "black box" nature of some AI models, the need for continuous retraining, or the difficulty in interpreting complex AI decisions in a clinical context.
   ***Answer*:** We would like to thank you for the valuable suggestion. We introduced further limitations such as the "black-box" nature of many AI systems, the requirement of large, high-quality datasets for training, as well as ongoing maintenance in the section "Current Challenges and Future Perspectives".

8. Patient Perspective: While the paper touches on improving patient quality of life, consider adding a brief discussion on the patient perspective regarding the integration of AI in their care. This could involve issues of trust, data privacy concerns from the patient's viewpoint, or the potential for increased access to care.
   ***Answer*:** Thank you for the comment. Therefore, in the section "Current Challenges and Future Perspectives" we added data concerning data privacy as well as the patient perspective.
9. Future Research Roadmap: In the "Future Perspectives," consider outlining a more concrete roadmap for future research, including specific areas that require immediate attention, interdisciplinary collaborations, or funding priorities
   ***Answer*:** As suggested, we introduced data about specific areas for future research in the final part of the section "Current Challenges and Future Perspectives".

Reviewer#3

Scientific Quality: Grade C (Good)

Language Quality: Grade C (Good)

Conclusion: Major revision

Specific comments to authors:

The manuscript covers a timely and important topic in gastroenterology. It demonstrates comprehensive knowledge of AI advancements in IBD care. However, several critical revisions are necessary, particularly regarding methodological transparency, balanced discussion, ethical implications, and language clarity.

1. The manuscript provides a broad and well-structured overview of artificial intelligence (AI) applications in the diagnosis and management of inflammatory bowel disease (IBD), including endoscopic, histologic, therapeutic, and clinical trial contexts. However, some sections contain overlapping content, particularly in the discussion of AI-assisted endoscopy.
***Answer*:** Thank you for the supportive comment. Therefore, we restructured the sections about endoscopic and histologic assessment in IBD using AI. Please see the updated manuscript.
2.While this is a narrative review, it is essential to maintain transparency regarding the methodology used to identify and select the literature included. Currently, the manuscript lacks a clear explanation of the search strategy, inclusion and exclusion criteria, and data sources. I strongly suggest the authors include a brief methodological section—preferably under "Materials and Methods" or in the introduction—detailing how the literature was identified, which databases were searched, and what criteria were applied for inclusion.
***Answer*:** Thank you for the comment. We introduced the section "Materials and Methods".
3.Although the manuscript summarizes numerous AI applications across various domains of IBD, the tone is predominantly descriptive and lacks critical appraisal. Most studies are presented without adequate evaluation of their limitations, such as sample size, external validation, or risk

of overfitting. I recommend the authors include a more balanced discussion that highlights not only the strengths but also the methodological weaknesses of the cited AI models, which would enhance the scientific rigor of the review.

***Answer*:** Thank you for the supportive comment. We revised the studies and used a balanced discussion as suggested, focusing also on the weaknesses of AI models. Please see the sections **AI-ASSISTED ENDOSCOPIC EVALUATION IN IBD** and **AI IN HISTOPATHOLOGICAL EVALUATION OF IBD**

4.The review includes a wide variety of AI models, including convolutional neural networks (CNNs), random forest classifiers, and natural language processing tools. However, the manuscript does not sufficiently address how the heterogeneity in model architecture, input data, and validation strategies impacts clinical translation and comparability. I encourage the authors to add a paragraph discussing the implications of this variability and the need for standardization in model development and benchmarking.

***Answer*:** We appreciate the advice. We introduced data in the section CURRENT CHALLENGES AND FUTURE PERSPECTIVES, the influence of the heterogeneity of the models and the requirements for clinical translation.

5.The authors briefly mention the importance of data quality in AI performance, but the discussion is not developed in sufficient depth. There should be an expanded discussion on potential sources of bias—such as class imbalance, site-specific imaging protocols, or retrospective data—and how these biases could affect the generalizability and fairness of AI tools in clinical practice.

***Answer*:** Thank you for your comment. We introduced further discussion in CURRENT CHALLENGES AND FUTURE PERSPECTIVES regarding the risk of bias of AI models and the impact on clinical practice.

6.The manuscript includes useful tables summarizing AI models applied in various domains of IBD care. However, the visual presentation could be improved by including additional graphical representations, such as performance comparisons or timelines of model evolution. I also suggest that all acronyms and abbreviations in the tables and figures be fully defined in their respective legends to improve accessibility for non-specialist readers.

Answer: Thank you for your comment. We introduced a figure for the timelines of model evolution in the introduction. Furthermore, we revised all acronyms and abbreviations.

7.Although the manuscript touches on ethical and regulatory challenges associated with AI implementation, this discussion is brief and lacks specificity. The authors should expand this section to include topics such as informed consent for AI-assisted diagnostics, data privacy, algorithmic transparency, and liability in cases of AI-related diagnostic errors. Referring to established guidelines such as SPIRIT-AI or CONSORT-AI would add value.

Answer: Thank you for your comment. We developed the discussion regarding ethical factors of AI model, introducing information of the specific guidelines, SPIRIT-AI or CONSORT-AI.

8.A noticeable imbalance exists between the discussions on ulcerative colitis (UC) and Crohn's disease (CD), with a much greater emphasis on UC throughout the manuscript. To provide a more balanced and comprehensive review, I recommend that the authors include more information on

AI applications specifically developed or validated for CD, particularly in the context of transmural healing, capsule endoscopy, and postoperative recurrence prediction.

Answer: Thank you for your comment. Therefore, we introduced further studies in Table 2 regarding capsule endoscopy in CD and postoperative recurrence prediction in CD in Table 3. Moreover, we introduced data regarding the gap of the AI research in Crohn's disease in the section **AI IN HISTOPATHOLOGICAL EVALUATION OF IBD.**

9.The final section of the manuscript discusses future perspectives in a general way but lacks actionable recommendations. I suggest the authors reframe this section to provide specific and practical guidance for future research, such as advocating for multicenter data-sharing initiatives, emphasizing external validation requirements, and encouraging interdisciplinary collaborations between clinicians, data scientists, and ethicists.

Answer: Thank you for your comment. We introduced practical recommendations in the final part of the section CURRENT CHALLENGES AND FUTURE PERSPECTIVES.

10.The manuscript is generally well written but contains numerous long and complex sentences, as well as occasional grammatical and stylistic issues that hinder readability. I recommend a thorough language edit by a native English speaker or professional editor to improve clarity, reduce redundancy, and ensure that key points are communicated succinctly and effectively.

Answer: Thank you for your comment. The article has been revised by a professional editor.

We truly appreciate your feedback, which has helped enhance the manuscript.