

Peer Review File

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Reviewer A

1) The control group did not include any CRC patients, but there is no guarantee that there were no cancers in other organs. The number of cases in this study was small, so this may have caused a bias.

Reply: Thank you for your comment. We employed rigorous exclusion criteria, thereby excluding subjects with tumors not related to CRC. Consequently, we ensured that no subjects within the control group developed malignant tumors. Although the sample size may appear relatively small, we have precisely determined that it meets the minimum requirement necessary for the application of machine learning algorithms.

Changes in the text: none

2) Line 90 ~: The disadvantages of colonoscopy, CT colonography and the fecal occult blood test are stated. The accuracy, sensitivity, specificity, positive 36 0.664 and negative predictive value of these methods should be compared with the method in this study. There is also expected to be a difference in the detection rate at an early stage colorectal cancer.

Reply: As previously mentioned, the comparative analysis of diverse tests can yield comprehensive data instrumental in the early detection of Colorectal Cancer (CRC). This information is invaluable to clinicians in selecting the most effective method for early CRC screening. However, numerous studies have already been conducted to investigate the diagnostic efficacy of these methods. The primary focus of this paper is to elucidate the diagnostic performance of centralized machine learning algorithms. Due to space constraints within this article, a comprehensive comparison of the diagnostic performance of various methods is not feasible. Nonetheless, the advantages and disadvantages of each method have been thoroughly discussed in the subsequent section.

Changes in the text: none

Reviewer B

Thanks for inviting me to review this interesting manuscript entitled " Construction of diagnostic models with machine-learning Algorithms for colorectal cancer based on clinical laboratory parameters". The authors aimed to develop a diagnostic model for

CRC that integrated various routine laboratory parameters, representing an important issue in the field.

However, the following points need attention:

- The abstract and the introduction are too long, kindly revise and be concise.

Reply: The abstract comprises 295 words, thereby fulfilling the journal's stipulated criteria. Furthermore, the introduction section adequately delineates the present circumstances and its word count is also in compliance with the journal's guidelines.

Changes in the text: none

- To the study populations, add the type of study.

Reply: We defined this study as retrospective in the Methods section.

Changes in the text: Methods section/Paragraph 1

- Add a flowchart representing the included participants for easier presentation.

Reply: A flowchart has been numbered as **Figure 1**

- Kindly explain how you selected the healthy control group and if a colonoscopy was done for these patients to exclude CRC and benign colonic polyps. And what about patients with inflammatory bowel diseases (IBD), an important risk for CRC development, could this model be applicable to the early detection of CRC in these patients?

Reply: All neoplasms, whether benign or malignant, were authenticated through pathological examination and immunodiagnostic procedures. Furthermore, individuals suffering from severe immunodeficiency disorders, such as Inflammatory Bowel Disease (IBD), were excluded from the study due to the potential influence of IBD on the clinical parameters under consideration. The limited sample size of patients with early-stage Colorectal Cancer (CRC) introduces a degree of uncertainty into our predictive model for early CRC diagnosis.

Changes in the text: none

- The results and the discussion were well-written.

Reply: Thank you for your positive comment.

Reviewer C

The use of this type of diagnostic support always gives patients the unjustified certainty that they do not need to undergo a colonoscopy. The alternative would be an

identical study focusing on liquid biopsying of cancer cell DNA. This would make sense with regard to an existing carcinoma, but not, of course, with regard to the detection of early precursors. But it is precisely these that would be important, because they do not affect the prognosis.

Reply: I concur with your assessment that the CRC diagnostic model we have developed may inadvertently lead potential CRC patients to believe that a colonoscopy is unnecessary. Nevertheless, it is imperative to first delineate the specific application context of this model. It is important to emphasize that this model is not intended to serve as the gold standard for CRC diagnosis; rather, it functions as an auxiliary diagnostic tool. This model can be effectively utilized within the population undergoing routine physical examinations and can facilitate the further stratification and diagnostic evaluation of individuals at high risk for CRC. Furthermore, the primary importance of this model lies in the scientific relevance of machine learning algorithms, which effectively integrate clinical indicators with computational techniques, thereby significantly advancing the clinical application of interdisciplinary approaches. Despite certain limitations in our study, such as a small sample size and constraints in the study parameters, we maintain that this model holds substantial scientific validity. Consequently, we assert that, given the current technological landscape, this model possesses broader application potential and greater scientific significance than its clinical counterparts.

Changes in the text: none