

Dear Editor and Reviewers,

It is with excitement that I resubmit to you a revised version of the manuscript “Preoperative neutrophil-to-lymphocyte ratio as a predictor of postoperative symptomatic anastomotic leakage in elderly patients with colon cancer: a multicenter propensity score-matched analysis” for the *Journal of World Journal of Gastrointestinal Surgery*. Thank you for giving us the opportunity to revise and resubmit this manuscript. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper. We have incorporated most of the suggestions made by the reviewers. **Those changes to the paper are highlighted or indicated with yellow color in the revised manuscript.** In addition, we also complied with your comments and sent the revised manuscript to a professional English language editing company to polish the manuscript further. We hope that the revision is acceptable and look forward to hearing from you soon.

Special thanks to you for your good comments. With best wishes.

Sincerely yours,  
Yongjiang Yu

Below, please find the comments in black, followed by our point-by-point responses in red. Exact changes in the manuscript are also presented in yellow font.

**Reviewer # 1**

**Comment 1:**

NLR is influenced by recent infections (especially COVID-19). Were individuals with recent infections or post-COVID syndrome excluded from the study?

**Response 1:**

Thanks for your comments. We totally understand your concern.

Patients admitted from January 2018 to December 2022 were included in this study. Between January 2018 and December 2019, China did not have a COVID-19 epidemic at that time. When COVID-19 emerged, the Chinese government and hospitals took strict control measures accordingly, and the three medical centers in this study were no exception. From the beginning of the COVID-19 outbreak, any patient (except for patients with acute and severe illnesses) had to be routinely tested for the virus before being hospitalized, and only patients who were not infected with COVID-19 were allowed to be admitted. In addition, admitted patients must be retested daily for COVID-19 antigen test during their hospitalization, and in case of positivity they are referred to an infectious disease hospital for further treatment. Therefore, all patients included in this study were not infected with COVID-19.

**Comment 2:**

NLR is influenced by special medications (steroids/ Biologics). Were subjects with recent medications (like IBD patients receiving anti TNF) excluded from the study?

**Response 2:**

We are extremely grateful to you for pointing out this problem.

Due to this study's inclusion criteria, only elderly patients with primary colon cancer were enrolled, and patients with inflammatory bowel disease (IBD) receiving anti-TNF therapy were not included, as you mentioned. Additionally, as per your suggestion, we have reevaluated patients' use of nonsteroidal

drugs and neoadjuvant chemotherapy in this study. Consequently, we have conducted a revised statistical analysis, and specific modifications are highlighted with yellow color in the revised manuscript.

**Comment 3:**

Are anatomical risk factors for leakage considered in the study?

**Response 3:**

We feel great thanks for your professional review work on our article.

Postoperative anastomotic leakage is a serious complication following colorectal surgery, influenced by various anatomical factors, including blood supply issues, anastomotic technique, and colorectal anatomy.

Regarding blood supply issues, we adhere to standard curative surgical procedures in all surgeries, ensuring neither excessive nor insufficient local vessel dissection. Exceeding the standard excision of local vessels may impact local blood supply at the anastomotic site. Conversely, in order to avoid a decrease in local blood supply to the anastomosis, inadequate local vessel dissection may fail to achieve curative objectives. Thus, strict adherence to curative surgical standards is maintained during operations. Additionally, studies suggest that intraoperative indocyanine green angiography can prevent insufficient blood supply and, consequently, anastomotic leakage. In the three medical centers involved in this study, routine indocyanine green angiography has not been performed from 2018 to 2022. Starting in 2023, these centers gradually introduced intraoperative indocyanine green angiography; however, due to national healthcare policies and patient financial constraints, routine implementation of this technique may be limited.

Regarding anastomotic technique issues, this study considers that the method of anastomosis of intestinal breaks may impact the occurrence of anastomotic leakage after colorectal cancer surgery. Furthermore, in these three medical centers, surgeons utilize anastomotic staplers for intestinal anastomosis in colorectal cancer surgeries, and because of being unaffected by space constraints, routine reinforcement sutures are applied to the anastomotic site to prevent leakage, making it impossible to compare with manual anastomosis or the use of reinforcement sutures.

Addressing colorectal anatomy issues, we recognize that tumor location and size may affect surgical and anastomotic approaches, thereby influencing the occurrence of anastomotic leakage after colorectal cancer surgery. Hence, this study analyzes the relationship between the location and diameter of colon tumors and the occurrence of anastomotic leakage following colon cancer surgery.

**Comment 4:**

Does the criteria used for the identification of leakage influence the results? If barium studies were used as end points the study might got different results.

**Response 4:**

Thanks for your meaningful comments. We strongly agree with you that barium contrast examination can definitively diagnose the occurrence of anastomotic leakage. In this study, our study outcome was symptomatic anastomotic leakage, and the diagnostic criteria were: first, abnormal fluid (e.g., pus, intestinal contents, etc.) discharged from a postoperative abdominal drain, and second, abdominal CT or contrast enema showing fluid or gas collection around the anastomosis. The contrast agent we use is barium, but not all patients undergo a barium contrast examination. This is because some patients can be clearly diagnosed based on the abnormal fluid coming out of the abdominal drainage tube, and in order to reduce the financial burden on the patient, no further barium contrast examination will be

performed. Only when the patient is suspected of anastomotic leakage, we will conduct barium contrast examination to further clarify the diagnosis.