

**Peer-Review Report(s).** Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s):

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade C (Good)

**Conclusion:** Minor revision

**Specific Comments to Authors:**

This study focuses on the clinical challenge of preoperative risk assessment in elderly patients with colorectal cancer, and its topic has significant clinical translational value. By exploring the predictive power of readily available indicators such as metastatic risk factor (mFI) and surgical risk factor (SII), the authors provide a useful reference for optimizing perioperative management in elderly patients. The overall study design conforms to retrospective research standards, and data collection is comprehensive, covering general patient information, tumor characteristics, laboratory indicators, and follow-up information. The statistical methods used are generally appropriate. Particularly noteworthy is the finding that the combination of mFI and SII is superior in predicting postoperative complications, a finding that has positive implications for improving the accuracy of clinical risk stratification. Suggestions for improvement: This study is a single-center retrospective design, and all included cases are from tertiary hospitals, limiting the representativeness of the sample and making it difficult to reflect the actual situation of elderly CRC patients in primary healthcare institutions. Furthermore, the study did not adequately control for key confounding factors such as preoperative nutritional status, surgical method (laparoscopic vs. open), and concomitant medications, which may directly affect the occurrence of postoperative complications and survival outcomes. It is recommended to supplement the study with propensity score matching analysis to reduce bias, or to further elaborate on these potential influencing factors and the reasons for

their exclusion from the analysis in the discussion section. Secondly, the SII cutoff value used in this study (927.45) differs significantly from that used in several previous studies (such as 451.05 by Sun et al. and 340 by Chen et al.). The authors simply attributed this to different study designs, failing to conduct an in-depth analysis considering the physiological characteristics of the elderly population, such as diminished immune function and chronic inflammation. It is recommended that the discussion further elucidate the specificity of this cutoff value in the elderly population and supplement the analysis with the predictive efficacy of SII in different tumor stages and age subgroups to clarify its applicability. Furthermore, the discussion section is somewhat weak in exploring the underlying pathophysiological mechanisms. Currently, it only describes the independent roles of mFI and SII separately, without analyzing whether there is an interaction between the two—for example, whether high mFI exacerbates elevated SII, or whether the superposition of the two leads to a worse prognosis. It is recommended that the discussion at the mechanistic level be further deepened, taking into account recent research progress on the association between frailty and systemic inflammatory response in the elderly.

Reply:

Thank you very much for your valuable feedback on this study.

1. The limitations of single center retrospective design and insufficient control of key confounding factors you raised are very relevant. We have described the limitations of the research in the article, but in order to more comprehensively address your concerns, we have further supplemented and refined the discussion section, as follows:

① Regarding the issue of sample representativeness. The cases included in this study all came from tertiary medical centers, which indeed limits the representativeness of the sample and makes it difficult to fully reflect the actual situation of elderly colorectal cancer patients in primary healthcare institutions. Patients in tertiary hospitals typically have more complex conditions and more

comprehensive preoperative evaluations, which may differ significantly from the patient population in primary hospitals. In addition, the medical resources and surgical techniques of tertiary hospitals are relatively advanced, and their ability to handle surgical complications is also stronger, which may lead to certain biases in the research results. Therefore, we further emphasized this limitation in the discussion section and pointed out that future research needs to be validated in a wider range of medical institutions to improve the generalizability of research results.

② Regarding the control of confounding factors. The preoperative nutritional status, surgical methods (laparoscopic versus open), and accompanying medications that you mentioned may indeed directly affect the occurrence of postoperative complications and survival outcomes. We were unable to fully control for these confounding factors in our study, mainly due to the following reasons: a. Preoperative nutritional status: Although we collected serum albumin and other indicators from some patients, they were not included in the final analysis due to differences in data completeness and recording methods. In addition, the lack of unified nutritional assessment standards (such as NRS-2002 or GLIM) also limits our comprehensive assessment of nutritional status. In future research, we will use standardized nutritional assessment tools to more accurately reflect the preoperative nutritional status of patients. b. Surgical methods (laparoscopic and open): Although surgical methods may theoretically affect the incidence of postoperative complications, in this study, due to the high proportion of laparoscopic surgery (over 90%) and the small sample size of open surgery, we were unable to fully evaluate their impact statistically. In addition, the choice of surgical method may be influenced by multiple factors, including the specific condition of the patient, the experience of the surgical team, etc., which further increases the complexity of the analysis. In future research, we will use methods such as multi center design and propensity score matching to more accurately evaluate the impact of surgical methods on postoperative outcomes. c. Accompanying medication: We

recorded the patient's preoperative medication use, but due to the lack of detailed information on medication dosage and duration, as well as the diversity of indications for medication use, we were unable to include it in the final analysis. In future research, we will record patients' medication use in more detail and use standardized drug classification methods (such as ATC coding) to better control for this confounding factor.

We have provided a detailed explanation of the above issues in the limitations section of the discussion, and emphasized the need for future research to be validated in a wider range of medical institutions and to adopt stricter methods to control confounding factors in order to improve the reliability and universality of research results.

2. The question you raised about the difference in SII threshold values is very important, especially in the elderly patient population, as this difference may be closely related to the physiological characteristics of the elderly. The following is a further explanation of this issue in our discussion section: We added "For instance, the immune function decline and chronic inflammatory state are more pronounced in the elderly population, which may lead to a difference in the distribution of SII values compared to younger patients or the general population. The immune system of the elderly exhibits a phenomenon known as "immunosenescence", characterized by a decline in lymphocyte function, changes in neutrophil activity, and elevated levels of chronic inflammatory markers. These changes may cause the SII values of the elderly to be at a relatively high level under normal physiological conditions, thereby affecting the determination of the critical value. Although we did not conduct further analysis on the predictive efficacy of SII in different tumor stages and age subgroups, existing studies have shown that the higher the tumor stage, the more significant the inflammatory response in patients. In elderly CRC patients, this inflammatory response may be further exacerbated, leading to an increase in SII values. Therefore, the SII cutoff values may need to be further calibrated in different tumor stages and age subgroups."

3. The discussion section you pointed out does have shortcomings in exploring potential pathophysiological mechanisms, especially in analyzing the interaction between mFI and SII. Based on your suggestion, we have supplemented and deepened the discussion section as follows: In elderly patients with colorectal cancer, the combined effect of mFI and SII may significantly influence the risk of postoperative complications and prognosis through multiple mechanisms. The frail state (high mFI) not only directly weakens the patient's physiological reserve and tolerance to surgical stress, but may also indirectly increase the SII value by exacerbating chronic inflammatory responses. Conversely, the systemic inflammatory state reflected by high SII will further deplete the patient's physiological reserve and weaken the immune defense capacity, thus forming a vicious cycle. The combination of the two not only significantly increases the risk of postoperative complications, but may also shorten the patient's recurrence-free survival period. Our research results show that the predictive efficacy of combining mFI and SII is superior to that of a single indicator (AUC = 0.941), which further supports the possible synergistic effect between the two.”

Thank you again for your valuable feedback. We will continue to work hard to improve the research design in order to provide a more scientific basis for the clinical management of elderly CRC patients.