

Dear *Editors and Reviewers of World Journal of Gastrointestinal Surgery*:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "*Predictive value of frailty assessment tools in patients undergoing surgery for gastrointestinal cancer: An observational cohort study*" (ID: 86320). All of the comments are all valuable and incredibly helpful in the revision and improvement of our paper. The feedback is also important in guiding the significance of our research. We have studied the comments carefully and have made corrections to our paper, which we hope will be met with approval. Revised portions are marked in yellow in the paper. The main corrections and our responses to the reviewer's comments are as follows:

Reviewer #1:

1. Response to comment: *English should be polished.*

Response: Thanks for your suggestion. We have invited a native English speaker from the biomedical editing company to polish our article. We hope the revised manuscript will be acceptable.

2. Response to comment: *What is your perspective based on the results in this study in the future?*

Response: Thank you for asking this question. Based on our study, more long-term outcome measures (including relapse-free survival time and overall survival) should be of interest. In addition, there is an urgent need for a pre-rehabilitation program which is suitable for China's national conditions to improve preoperative frailty in patients undergoing gastrointestinal cancer surgery. We have added this to the manuscript (Line, page).

3. Response to comment: *How do you manage the patients with abnormalities of CGA in performing surgery for gastrointestinal cancer?*

Response: Thank you for pointing this out. We hope to form a multidisciplinary team consisting of nutritionists, psychologists, rehabilitation therapists,

gastrointestinal surgeons and nurses to help patients develop personalized pre-rehabilitation measures that can be implemented at home, in the hospital or a combination of both. We should improve the frail state of patients before operation with as little expenditure as possible in order to reduce hospitalization expenses for patients. A pre-rehabilitation program suitable for China's national conditions is urgently needed. We have added the above based on your recommendation (line, page).

4. Response to comment: *The cutoff value of B.I. <100 is too high.*

Response: Thank you for pointing this out. Generally, this may be a high cutoff. However, it has been shown in most studies that B.I. in the CGA assessment is mostly set at a cutoff of < 100, which may be related to the peculiarity of the CGA [1-3]. We set a cutoff based on previous studies that may be more favorable for comparison with other studies. However, it should be noted that the question of whether the cutoff values for each scale in the CGA are reasonable is considered to need further exploration in subsequent studies.

5. Response to comment: *How about the relationship between the scores of three tools and prognostic factors such as recurrent-free survival time or overall survival?*

Response: Thank you for your suggestion. Recurrence-free survival time and overall survival are important outcome measures for cancer patients and should be of concern. However, these outcome measures cannot be collected in the short term. We regret this, but hope to explore their correlation in future research. We have added the above based on your recommendation (Line, page).

6. Response to comment: *Line number should be restarted from one in every page.*

Response: Thank you for pointing this out. We have recoded the line number.

7. Response to comment: *In the results section, I recommend that baseline patients characteristics are shown and described firstly.*

Response: Thank you for your suggestion. We have placed baseline patient

characteristics at the beginning of the results (Line, page).

Special thanks to you for your good comments.

-----End of Reply to Reviewer#1-----

Reviewer #2:

1. Response to comment: *The bias was to consider only postoperative complications that developed during hospitalization: the effect of frailty can be evident within 30 days from surgery and the considered cut-off is in effect a huge study limitation and the possible explanation of the following result: None of the frailty assessment tools were associated with postoperative complications.*

Response: Thank you for pointing this out. When designing the study, we chose the Clavien-Dindo classification, which is more commonly used in patients with gastrointestinal cancer as evaluation criteria [4, 5]. It focuses on methods of grading by complication treatment measures and is often used for the evaluation of in-hospital complications [5, 6]. Importantly, the data obtained through the hospital information system can ensure its authenticity and accuracy. One previous study showed that 6% of patients have no complications at discharge but developed complications after discharge, with the most common complication grade being Clavien-Dindo II [7]. This is consistent with your opinion. Unfortunately, we did not collect the incidence of complications after discharge. Based on comments from another reviewer, we changed severe complications (Clavien-Dindo \geq III) to the outcome measure. The majority of severe complications occur in hospitals and have a greater impact on the recovery of patients, which then requires a high amount of attention. We have revised the manuscript accordingly based on the above discussion and hope to meet your requirements.

2. Response to comment: *The employed tools investigate functional and cognitive aspects, and consider malnutrition only by assessing weight loss.*

Response: Thank you for pointing this out. Our study assessed malnutrition

status by a Patient-Generated Subjective Global Assessment (PG-SGA). As a part of CGA, this is a specific assessment tool used to for the nutritional status of cancer patients. Weight loss is part of Fried phenotype (FP), and its authors may want to use this indicator to determine whether patients are at risk of malnutrition. We apologize for not being clear in the manuscript and have now made the corresponding modifications.

3. Response to comment: *I do not agree that it is necessary to explore patients' frailty across all ages, as in younger ages the nutritional issues are the main concern.*

Response: Thank you for pointing this out. We agree that malnutrition may be a major problem in young patients rather than frailty. However, malnutrition and frailty may be interacting [8]. Frailty is defined as a state that is highly susceptible to stressors, leading to adverse health outcomes. Although it is generally considered an age-related syndrome, we believe that the assessment of frailty should probably not be limited by age. This view has also been reported in previous studies and guidelines [3, 9, 10]. Ethun et al. [11] pointed out that frailty often overlaps with incapacity and chronic diseases, and patients are at greater risk of disability and frailty when chronic diseases include cancer. This means that cancer itself may be more likely to increase the prevalence of frailty. Therefore, it may occur more frequently in younger patients. In addition, gastrointestinal cancers have accounted for 45% of cancer-related deaths in China [12], and the incidence of cancer is getting younger and younger. Frailty assessments may extend from elderly patients to patients of all ages, which helps to find more young frail patients. They may return to work after surgery, and reducing the occurrence of adverse outcomes due to frailty has very important practical significance at both the social level and the patient's personal level. Exploring the predictive value of age wide frailty for adverse outcomes may have more general implications. But in the previous manuscript, we described frailty assessment for all ages as an advantage, which was inappropriate. We have now deleted this section and hope to meet your requirements.

4. Response to comment: 83 (36.2%) patients had gastric cancer, 81 (35.4%) had colon cancer, and 65 (28.4%) had rectal cancer: these three clinical situations are linked to a slightly different metabolic upset in terms of malnutrition and sarcopenia, so a bias in this analysis can be speculated.

Response: Thank you for pointing this out. We performed univariate analysis of these three clinical conditions as confounding factors that could influence the occurrence of frailty in patients, and the results showed that cancer type may have an effect in frailty assessed by the CGA, but no statistical difference was shown in the Fried phenotype and FRAIL scale. It is meaningful to analyze for different diseases. However, due to our limited resources, we cannot collect more samples in the short term, which makes it impossible for us to analyze them separately. This is a limitation of our study. We have added this point of view to the discussion.

5. Response to comment: I agree that such patients are more vulnerable to frailty due to cancer cachexia, cancer-related fatigue and gastrointestinal symptoms: however to state that these latter contribute to the high prevalence of frailty in this population is too generic, as malnutrition, sarcopenia and cachexia are not synonyms, and the concept of frailty has a wider acception.

Response: Thank you for pointing this out. Our description of this paragraph may not be appropriate and has now been revised to "Due to the inherent and therapeutic factors of gastrointestinal cancer, these patients are more susceptible to stress on their physiological and psychological reserve abilities, leading to adverse outcomes", see (line, page).

6. Response to comment: I think that to consider emergency surgery or palliation is a powerful confounding factor in evaluating frailty assessment and must not be considered.

Response: Thank you for pointing this out. We consider that emergency and palliative surgery patients are critically ill, and patients and their families may

not allow us to complete the collection of data. Moreover, our survey was relatively long, which may delay the treatment of such patients and cause physical and mental damage, so we did not consider them as part of the research population. This is a limitation of our study and I hope our response is satisfactory to you.

Special thanks to you for your good comments.

-----End of Reply to Reviewer#2-----

Reviewer #3:

1. Response to comment: *Was your sample underpowered? Did you calculate the sample size before inclusion?*

Response: Thank you for pointing this out. We apologize for not adding sample size to the manuscript. We calculated the sample size for postoperative severe complications based on a previous study [13], and the complication rate was 43% in frail patients and 17% in non-frail patients. We set an α -value of 0.05 and a power of 80% to calculate that 96 patients should be included in the study. We have added the above to the manuscript.

2. Response to comment: *How do you explain such a difference in frailty prevalence (CGA, Fried phenotype, and FRAIL scale: 65.9%, 47.6%, and 34.9%, respectively)?*

Response: Thank you for pointing this out. Because these assessment tools differ in terms of items and dimensions, there are clear differences in the results of the frailty assessment. As such, our study hopes to investigate their predictive value for adverse outcomes and to identify which tool is most relevant. We have added the above to the manuscript.

3. Response to comment: *You also excluded "patients who were unable to cooperate with and complete data collection". Does this mean that patients who were not able to complete the FRAIL scale were all excluded? This might be an important bias, as a patient who cannot communicate can be the most frail.*

Response: Thank you for pointing this out. We excluded situations in which the survey was actively interrupted by the patient for various reasons. Some of these populations may be frail, but we may not be able to continue the investigation based on the principle of respecting the patient's wishes. This is a limitation of our study as such populations should also be of concern.

4. Response to comment: *If you considered major complications only (Clavien Dindo higher or equal to 3), do you think it would show a more significant difference between groups?*

Response: Thank you for pointing this out. Taking into account a previous reviewer and your suggestions, we replaced the severe complication (Clavien Dindo ≥ 3) with the overall complication for statistical analysis, which is mainly reflected in **Table 3**. Although our results showed that none of the three frailty assessment tools predicted the incidence of severe complications, this did make sense for our study protocol. We are very grateful for that.

5. Response to comment: *Also, you might want to include "Sandini M, Pinotti E, Persico I, Picone D, Bellelli G, Gianotti L. Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery. BJS Open. 2017 Nov 9;1(5):128-137. doi: 10.1002/bjs5.22. PMID: 29951615; PMCID: PMC5989941." in your references.*

Response: Thank you for the reference, which are now included in the revised manuscript, see Ref 11.

6. Response to comment: *The ARRIVE guidelines are for Animal Research: Reporting of In Vivo Experiments, you should change this on your manuscript accordingly.*

Response: Thank you for pointing this out. We are very sorry for our incorrect writing, which are now changed in the revised manuscript.

Special thanks to you for your good comments.

-----End of Reply to Reviewer#3-----

Reviewer #4:

1. Response to comment: *Karnofsky score is also viewed as a frailty assessment tool in a general sense, authors should also explore its value*

Response: Thank you for your suggestion. In past studies, the Karnofsky score has been used to assess frailty. But now more people see it as a tool to assess the functional status of cancer patients. The guidelines developed by the 2019 International Conference on Frailty and Sarcopenia did not include Karnofsky score in the assessment tool for frailty [14]. But undeniably, the Karnofsky score is very important. We have included it as a confounding factor that may influence the incidence of outcome measures and performed statistical analysis.

2. Response to comment: *When adopting a frailty scale designed on a different population, than in the present study, authors should come-up with their own cut-off of frailty, valid on their population of interest. So, why not exploring the predictive value of 75th or 80 percentile of any frailty scale they have chosen.*

Response: Thank you for your suggestion. The scales we chose were all widely used, well-established scales. They go through a rigorous standardization process with fixed dimensions and statistical methods. If we develop our own scoring methods, the results obtained may not be comparable to other people's studies. In previous studies, they have also used the original authors' scoring method [1, 15]. However, this is indeed a worthwhile direction for research, suggesting that we can develop a frailty assessment tool suitable for the population we focus on and set appropriate cutoff values.

Special thanks to you for your good comments.

-----End of Reply to Reviewer#4-----

Reviewer #5:

1. Response to comment: *But the text should explain why it is important to predict adverse postoperative outcomes.*

Response: Thank you for your suggestion. Identifying the factors that affect the adverse outcomes of patients can help us recognize the importance of evaluation and provide a theoretical basis for formulating corresponding intervention measures. We have added the above to the manuscript.

2. Response to comment: *Why assessing frailty is relevant to this prediction.*

Response: Thank you for your suggestion. It should be noted that frail patients may increase the incidence of severe complications due to their decreased ability to cope with stress, and frailty has the potential to compromise patient recovery following surgery, thereby increasing the cost of associated treatment, care and medications. To date, there are few reports on these two outcome measures. So, they need to be highly valued. We have added the above to the introduction.

3. Response to comment: *Expanding on the practical implications of the study's findings for clinical practice and patient care would make the conclusion more impactful.*

Response: Thank you for your suggestion. It is hoped that our study will arouse the attention of health care providers and the CGA should be included as part of routine preoperative risk assessment in patients undergoing surgery for gastrointestinal cancer. In addition, we hope to form a multidisciplinary team including nutritionists, psychologists, rehabilitation therapists, gastrointestinal surgeons, and nurses to help patients develop personalized pre-rehabilitation measures, which can be implemented at home, in the hospital, or a combination of both. We should improve the frail state of patients before their operations with as little expenditure as possible in order to reduce the hospitalization expenses of patients. A pre-rehabilitation program suitable for China's national conditions is urgently needed now. We have added this part to the manuscript.

Special thanks to you for your good comments.

-----End of Reply to Reviewer#5-----

Responds to the **Company editor-in-chief** comments:

1. Response to comment: *I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.*

We tried our best to improve the manuscript and made some changes in the manuscript. And here we did not list the changes but marked in yellow in revised paper.

Response: Thank you for your suggestion. We have added some influential papers to the manuscript. This is indeed a great database, and we are very grateful for it.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions. Looking forward to hearing from you regarding our submission!

Sincerely,

Hailin Zhang

References:

1. Tsai CY, Liu KH, Lai CC, Hsu JT, Hsueh SW, Hung CY, Yeh KY, Hung YS, Lin YC, Chou WC: **Association of preoperative frailty and postoperative delirium in older cancer patients undergoing elective abdominal surgery: A prospective observational study in Taiwan.** *Biomed J* 2023, **46**:100557.
2. Hung CY, Liu KH, Tsai CY, Lai CC, Hsu JT, Hsu CC, Hung YS, Chou WC: **Impact of preoperative frailty on the surgical and survival outcomes in older patients with solid cancer after elective abdominal surgery.** *J Formos Med Assoc* 2023.
3. Chen SY, Chou WC, Lin YC, Tsang NM, Liao KC, Lin CH, Lin JR, Ho YW, Tang WR: **Performance of two frailty screening tools among patients with cancer in Taiwan.** *Biomed J* 2022, **45**:361-369.
4. Ogata T, Sadakari Y, Nakane H, Koikawa K, Kanno H, Kohata R, Endo K, Tsukahara T, Shimonaga K, Kaneshiro K, et al: **The five-item modified frailty index predicts long-term outcomes in elderly patients undergoing colorectal cancer surgery.** *World J Surg Oncol* 2023, **21**:268.
5. Ding L, Miao X, Lu J, Hu J, Xu X, Zhu H, Xu Q, Zhu S: **Comparing the Performance of Different Instruments for Diagnosing Frailty and Predicting Adverse Outcomes among Elderly Patients with Gastric Cancer.** *J Nutr Health Aging* 2021, **25**:1241-1247.
6. Mazzotta AD, Kawaguchi Y, Pantel L, Tribillon E, Bonnet S, Gayet B, Soubrane O: **Conditional cumulative incidence of postoperative complications stratified by complexity classification for laparoscopic liver resection: Optimization of in-hospital observation.** *Surgery* 2023, **173**:422-427.
7. Ommundsen N, Nesbakken A, Wyller TB, Skovlund E, Bakka AO, Jordhoy MS, Rostoft S: **Post-discharge complications in frail older patients after surgery for colorectal cancer.** *Eur J Surg Oncol* 2018, **44**:1542-1547.
8. Cruz-Jentoft AJ, Woo J: **Nutritional interventions to prevent and treat frailty.** *Curr Opin Clin Nutr Metab Care* 2019, **22**:191-195.
9. Michaud MM, English WJ, Nandakumar M, Li CJ, Dvorkin L: **The impact of frailty on clinical outcomes in colorectal cancer surgery: A systematic**

literature review. *Anz J Surg* 2021.

10. Partridge J, Ryan J, Dhesei JK: **New guidelines for the perioperative care of people living with frailty undergoing elective and emergency surgery-a commentary.** *Age Ageing* 2022, **51**.

11. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA: **Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology.** *CA Cancer J Clin* 2017, **67**:362-377.

12. Cao W, Chen HD, Yu YW, Li N, Chen WQ: **Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020.** *Chin Med J (Engl)* 2021.

13. Mazzola M, Bertoglio C, Boniardi M, Magistro C, De Martini P, Carnevali P, Morini L, Ferrari G: **Frailty in major oncologic surgery of upper gastrointestinal tract: How to improve postoperative outcomes.** *Eur J Surg Oncol* 2017, **43**:1566-1571.

14. Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodriguez-Manas L, Fried LP, Woo J, Aprahamian I, Sanford A, Lundy J, et al: **Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management.** *J Nutr Health Aging* 2019, **23**:771-787.

15. Ogata T, Sadakari Y, Nakane H, Koikawa K, Kanno H, Kohata R, Endo K, Tsukahara T, Shimonaga K, Kaneshiro K, et al: **The five-item modified frailty index predicts long-term outcomes in elderly patients undergoing colorectal cancer surgery.** *World J Surg Oncol* 2023, **21**:268.