

Peer Review File

Article information: <https://dx.doi.org/10.21037/jgo-23-543>

Reviewer A

1. Malnutrition diagnosed using GLIM criteria will be associated with clinical outcome. This is not news. However, it is still worthwhile to compare the prognostic value of GLIM criteria to other criteria. Comparing GLIM to competitor criteria would lead ahead on the road to establish GLIM as a valuable concept to diagnose malnutrition. Without such comparison little new knowledge is generated.

Reply 1: GLIM integrates NRS2002 score, body weight, BMI, and muscle mass, and is a comprehensive nutritional risk assessment indicator. Several articles have compared GLIM with other indicators such as MUST, PG-SGA, sarcopenia, etc. However, no articles have evaluated the effect of GLIM on nutritional risk assessment in elderly patients with colorectal cancer.

Changes in the text: None.

2. There is no primary outcome presented in the manuscript. However at least 72 statistical tests are reported. Without a primary outcome, the study needs to be labelled 'exploratory' throughout. In addition, an adaptation to multiple statistical testing should be done. As an example, with 72 tests, the threshold signifying statistical significance may be adapted according to $p < 0.05/72 = 0.0007$. At this level, none of the reported comparisons resulted in a statistical difference.

Reply 2: The primary outcome of the manuscript is that: GLIM malnutrition was an independent risk factor for post-operative complications and overall survival in elderly patients with CRC. This result was calculated by multivariate logistic regression and multivariate COX regression, and the interference of other synergistic factors has been excluded. In addition this study does not contain multiple primary efficacy indicators, or the comparison of differences between multiple groups, so there is no need to perform multiple hypothesis testing.

Changes in the text: None.

3. The authors repeatedly label GLIM criteria as 'new malnutrition screening criteria' (p2, line 40), as 'new nutritional status assessment tool' or 'criteria for the assessment of nutritional status' (p2, Highlight Box), 'tool in the evaluation of the nutritional status' (p 2, line 55), 'can accurately evaluate the nutritional status' (page 7, line 246) etc. I strongly recommend to stick with the wording that GLIM criteria are 'diagnostic criteria for malnutrition'.

Reply 3: OK, We have corrected these in the revised manuscript.

Changes in the text: We have modified our text as advised(see Page 2, line 49),(see Page 3, line 69),(see Page 3, Highlight Box).

4. GLIM diagnosis of malnutrition requires an etiologic criterion. While the authors

claim that the presence of a tumor is sufficient to fulfill the etiologic criterion of ‘disease burden/inflammation’ (page 4, line 127), careful reading of the consensus report on GLIM criteria (Cederholm T et al. Clin Nutr 2019) reveals that the decisive criterion is presence of acute or chronic inflammation. This may be measured by laboratory values or may be discerned clinically in many cases by the presence of ‘fever, negative nitrogen balance, and elevated resting energy expenditure’. However, ‘clinical judgement is often required to recognize lesser degrees.’ Thus, by assuming the presence systemic inflammation in all 385 patients, the authors will have overdiagnosed malnutrition in their study population.

Reply 4: The GLIM criteria did not clearly specify the definition of inflammation in the etiology criteria. As a malignant tumor of the gastrointestinal tract, gastrointestinal cancer has a great impact on the whole body. Studies showed that gastrointestinal cancer was strongly associated with inflammation [1, 2]. Therefore, we believe that GLIM criteria can have various interpretations according to the conditions of different centers. In the present study, all patients with gastrointestinal cancer were considered meeting the etiologic criteria of inflammation/disease burden. In addition, other studies on gastrointestinal cancer all assume that gastrointestinal cancer meet the etiological diagnostic criteria of GLIM[3].

Changes in the text: None.

[1] Montinaro A, Walczak H. Sterile Inflammation Fuels Gastric Cancer. *Immunity*. 2018;48:481-3.

[2] Fichtner-Feigl S, Kesselring R, Strober W. Chronic inflammation and the development of malignancy in the GI tract. *Trends Immunol*. 2015;36:451-9.

[3] Zhou LP, Yu DY, Ma BW, et al. Feasibility of substituting handgrip strength for muscle mass as a constituent standard in the Global Leadership Initiative on Malnutrition for diagnosing malnutrition in patients with gastrointestinal cancers. *Nutrition* 2021;84:111044.

[4] Song HN, Wang WB, Luo X, et al. Effect of GLIM-defined malnutrition on postoperative clinical outcomes in patients with colorectal cancer. *Jpn J Clin Oncol* 2022;52:466-74.

[5]Huang DD, Yu DY, Song HN, et al. The relationship between the GLIM-defined malnutrition, body composition and functional parameters, and clinical outcomes in elderly patients undergoing radical gastrectomy for gastric cancer. *Eur J Surg Oncol* 2021;47:2323-31.

There is a number of smaller points:

At several point, the authors state that GLIM criteria ‘is a feasible tool’ or ‘can be used’ (e.g. p 2, line 55, p2 Highlight Box). If no qualifier is given, then this statement is obvious but of no value.

Reply: We have changed these expressions in the revised manuscript.

Changes in the text: We have modified our text as advised(see Page 3, Highlight Box).

Page 3, lines 66-68: Two similar statements follow each other with vastly different deaths reported.

Reply: It is a mistake. We have corrected these in the revised manuscript.

Changes in the text: We have modified our text (see Page 3, line 81).

Page 3, line 88: The authors might reference the few studies which have explored GLIM criteria in elderly colorectal cancer patients previously.

Reply: "Few studies" is easily misunderstood as "a few studies", so we changed it to "there are no study explored the application of GLIM criteria in elderly colorectal patients" in the revised manuscript

Changes in the text: We have modified our text (see Page 4, line 104).

Page 3, line 89: It would be essential to present the parameters which were used to judge the effectiveness of a GLIM diagnosis (not 'screening').

Reply: We have changed the description accordingly: the purpose of this study was to use GLIM criteria to diagnose malnutrition in elderly patients who underwent curative CRC surgery and to analyze the impact of GLIM malnutrition on post-operative complications and long-term outcomes of patients.

Changes in the text: We have modified our text (see Page 4, line 105-108).

Page 4, line 111. I recommend to translate low albumin levels to 'hypoalbuminemia' instead of 'hypoproteinemia'.

Reply: We have changed these words in the revised manuscript.

Changes in the text: We have modified our text as advised (see Page 5, line 129),(see Page 9, line 262).

Reviewer B

1) In the abstract, the methods should not list the statistical methods used in the study but should describe what each method was used to examine.

Reply: Thank you, we have revised the manuscript according to the suggestions.

Changes in the text: We have modified our text as advised (see Page 2, line 55-59)

2) In the INTRODUCTION section, lines 66-68 are confusing.

Reply: It is a mistake. We have corrected these in the revised manuscript.

Changes in the text: We have modified our text (see Page 3, line 81).

3) As for exclusion criteria, please include a CONSORT diagram to show how many patients and why they have been removed from this study.

Reply: We have included a CONSORT diagram in the revised manuscript.

Changes in the text: We have modified our text (see Page 6, line 178-180),(see Page 19, Figure1).

- 4) The authors did multivariate analyses for postoperative complications and overall survival. However, there needs to be a discussion as to how the multivariate analysis models were designed. It appears that only factors significant in univariate were included in multivariate analysis, but this needs to be stated. There are many ways to select variables to be included in multivariate analysis (significant in univariate analysis, known to be clinically relevant, backward step-wise elimination, forward step-wise elimination, etc).

Reply: Only variables with a P value < 0.1 in the univariate regression analysis were included in the multivariate regression analysis. Multivariate regression analysis was performed using forward step-wise elimination.

Changes in the text: We have modified our text (see Page 6, line 170-172).

- 5) There are descriptions of "univariate and multivariate analyses showed ~independent risk factor", but the univariate analysis is not adjusted analysis, so independent factors cannot be detected. It would be better to correct the description.

Reply: We have corrected the description into "multivariate analyses showed ~independent risk factor".

Changes in the text: We have modified our text(see Page 7, line 202), (see Page 7, line 209).

- 6) As for postoperative complications, only the incidence of postoperative venous thrombosis was significantly higher in the GLIM-malnutrition group. However, the number of people with each complication is quite small due to the detailed breakdown of complications and may therefore not have reached statistical significance. It would be better to also analyze the classification of 'infectious complications', 'medical or surgical complications, etc.

Reply: We have analyzed the classification of surgical complications and medical complications.

Changes in the text: We have modified our text as advised(see Page 16, Table 2),(see Page7, line 198-200).

- 7) Tumor location (colon or rectum) is an important factor related to postoperative complications and prognosis. Tumor location should be included in the analysis and should also be included in the patient characteristics.

Reply: We have Tumor included location in the analysis and in the patient characteristics in the revised manuscript.

Changes in the text: We have modified our text as advised(see Page 16, Table 2), (see Page 17, Table 3), (see Page 18, Table 4), (see Page7,line 189).

- 8) In the present study, GLIM-malnutrition was related to OS but not to DFS. The authors mentioned that previous studies have reported a relationship with DFS, but these studies differ in the baseline characteristics of the cohort. Does this mean

that malnutrition may not affect recurrence or second cancer if there is no difference in patient background other than nutritional status? If malnutrition does not affect recurrence, what about the cause of death in the malnutrition group? Please clarify.

Reply: In a previous study exploring the impact of GLIM-malnutrition on overall colorectal cancer patients, patients with GLIM malnutrition had a higher TNM stage of tumor, a higher proportion of previous abdominal surgery and a lower proportion of laparoscopic surgery[1]. These clinical factors are closely related to tumor recurrence. In contrast, our study showed that malnutrition in elderly CRC patients was not associated with these clinical baseline indicators. Our findings suggest that GLIM-malnutrition has no effect on tumor recurrence in elderly colorectal cancer patients. In addition, our study shows that GLIM-malnutrition is an independent risk factor for post-operative complications. The occurrence of postoperative complications may affect the patient's chemotherapy tolerance, quality of life, and directly or indirectly lead to death. So our study suggests that GLIM-malnutrition may affect the overall survival rate of patients by affecting postoperative complications.

Changes in the text: None.

[1] Song HN, Wang WB, Luo X, et al. Effect of GLIM-defined malnutrition on postoperative clinical outcomes in patients with colorectal cancer. *Jpn J Clin Oncol* 2022;52:466-74.

9) An important limitation of this study is that the measurement of muscle mass according to the GLIM criteria was done by measuring grip strength. Recent recommendations from the GLIM working group advocate that muscle mass and function should be assessed separately (Barazzoni R, *Clin Nutr* 41:1425-1433, 2022). It would be preferable to describe this point in more detail.

Reply: Yes, this is a limitation of this article. In follow-up studies, we will take comprehensive indicators of muscle mass and muscle function, such as sarcopenia, as the indicators of muscle mass in the GLIM criteria.

Changes in the text: None.