Peer Review File

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Reviewer A

Introduction

Comment 1: How will ALI offer a therapeutic strategy?

Reply: thank you for your nice comment. ALI is sample, convenient, low-cost, and useful prognostic score, which based on BMI, ALI, neutrophil count, and lymphocyte counts. We found that low ALI value was correlated with worse prognosis (OS and CSS). For the patients with gastric cancer who underwent radical resection, the adjuvant therapy and surveillance project are parts of treatment strategy. Based on our findings, preoperative ALI may be useful to determine whether adjuvant therapy is needed and the therapeutic regimen.

Comment 2: What do the authors mean by high risk patients (line 65)? High risk of disease progression or mortality? High risk of surgical complications?

Reply: Thank you for your nice comment. The high risk means that patients have high risk with poor prognosis (mortality). In this study, we did not analysis the risk of surgical complications.

Comment 3: Line 67-68 should be referenced

Reply: thank you for your suggestion. We added the reference to support the sentence. (see Page 4, line 69-70)

Comment 4: Line 84 - 85 should be broken up unto smaller sentences. The fact GC often causes gastrointestinal symptoms is unrelated to the fact it is common.

Reply: thank you for your correction. We revised the sentence(see Page 4, line 86-87).

Changes in the text: GC may cause upper gastrointestinal symptoms, including nausea, vomiting, bloating, abdominal pain, etc. Therefore, nutritional impairment may be present in patients with non-metastatic GC.

Methods chapter is quite complete.

Discussion

Comment 5: More discussion is required on the limitations of the study.

Reply: thank you for your suggestion. According to your following suggestion and comment, we updated the limitation part (see Page 13-14, line 288-296).

Changes in the text: There are some potential limitations of this work. First, this is a retrospective and single-centre study, although we assess a larger sample of patients with non-metastatic GC. Therefore, several forms of bias, such as selection bias or observer bias, may have been present in this study. Secondly, we only focus on ALI at a single time point. And limited by retrospective study, we cannot obtain the dynamic of ALI at multiple time points. Furthermore, it is complicated to evaluate systemic nutrition. BMI and ALB were selected to evaluate systemic nutrition in the study, which might have some limitations with respect to

specificity and sensitivity. To overcome these limitations, a multi-centre and prospective study is needed to validate these results.

Comment 6: The ALI was taken at a single time point. Understanding ALI at multiple time points would be informative, but difficult in a retrospective study. This could be listed as a limitation and could be addressed in a prospective study

Reply: thank you for your kind comment. It is difficult for a retrospective study to observe the change of ALI at multiple time points. We discussed this point in the limitation part. In a prospective study, the dynamic of ALI at multiple time points will be an interesting and valuable topic.

Comment 7: BMI is not an effective measure of systemic nutrition however it is easy to measure. It would be worth describing the limitations of BMI as a measure

Reply: thank you for your suggestion. The methods to evaluate systemic nutrition include triceps skinfold thickness, mid-arm muscle circumference, waist circumference, Albumin, prealbumin, and plasma amino acid profile, and creatinine height index. As a single indicator, it is limited for BMI to evaluate nutritional status. Therefore, we discussed the limitation of BMI in the limitation part. (see Page 14, line 296-295)

Changes in the text: Furthermore, it is complicated to evaluate systemic nutrition. BMI and ALB were selected to evaluate systemic nutrition in the study, which might have some limitations with respect to specificity and sensitivity.

Comment 8: The mean BMI of this population is quite low (20 and 22). This is not comparable with other populations globally (such as Australia and US) where BMI is generally higher. This could be commented on.

Reply: thank you for your nice comment. The distribution of BMI in the Chinese population is different from the American or Australian populations. We discussed the topic in the Discussion part (see Page 12, line 256-260). The optimal cutoff of ALI was affected by the difference in BMI, so the cutoff of ALI in this study may apply to the Chinese population.

Changes in the text: According to epidemiological surveys, the mean BMI of the Chinese population is lower than that of the North American and Western European populations. The mean BMI is 22.13kg/m^2 in the present study, consistent with survey results. Therefore, the optimal cut-off of ALI in this study may apply to the Chinese population.

Comment 9: Line 279: The authors should expand on what they mean by 'more aggressive treatment'. Do they advocate for preoperative nutritional support to improve BMI? More aggressive oncological or surgical treatment?

Reply: thank you for your question. We found that low preoperative ALI was correlated with a worse prognosis. Based on the findings, we believe that patients with low ALI may be necessary to accept adjuvant chemotherapy or a more aggressive regimen after radical resection. For a clearer statement, we revised the sentence (see Page 12, line 256-260).

Changes in the text: The decreased ALI implies that patients with early-stage GC may require close follow-up, and patients with local advanced GC may require more aggressive adjuvant chemotherapy.

Conclusion

Comment 10: Line 286-288: There is another published paper (that is referenced) that demonstrated ALI as a prognostic marker. Is it true to say this was first demonstrated by your group? How does your paper add to their findings?

Yin, Chengzeng; Toiyama, Yuji; Okugawa, Yoshinaga; Omura, Yusuke; Kusunoki, Yukina; Kusunoki, Kurando; Imaoka, Yuki; Yasuda, Hiromi; Ohi, Masaki; Kusunoki, Masato (2020). Clinical significance of advanced lung cancer inflammation index, a nutritional and inflammation index, in gastric cancer patients after surgical resection: A propensity score matching analysis. Clinical Nutrition, (), S0261561420303836–. doi:10.1016/j.clnu.2020.07.018

Reply: thank you for your correction. Our statement may not be rigorous enough. We revised the sentence (see Page 14, line 298-299). This referenced paper analyzed the relationship between ALI and OS/DFS in the whole TNM stage of gastric cancer. But we focused on the relationship between non-metastatic gastric cancer (early-stage gastric cancer and locally advanced gastric cancer) and OS and CSS. This is part of what our study adds to the findings.

Changes in the text: In the study, we demonstrated that preoperative ALI was an independent prognostic marker in patients with non-metastatic GC underwent radical surgery.

Reviewer B

Generally, the manuscript is well-written and the issue is of moderate importance in clinical practice. However, there are some concerns regarding the methodology, listed as follows:

Comment 11: The authors used the title “Advanced Lung Cancer Inflammation Index Predicts Outcomes of Patients with Non-metastatic Gastric Cancer After Radical Surgical Resection". Formally, if you want to build up a prediction model, you have to validate your model using different datasets. Propensity score matching is not a validation method but a sensitivity test at best. Please revise.

Reply: thank you for your correction. We revised it (see Page 3, line 55).

Changes in the text: Further PSM analysis confirmed the prognostic value of ALI in the PSM cohort.

Comment 12: Abstract: Please present the hazard ratio and 95% confidence intervals for study outcomes instead of only p values.

Reply: thank you for your suggestion. We revised the abstract (see Page 3, line 52-54).

Changes in the text: Multivariable analysis showed that ALI was an independent prognostic factor for both OS (HR = 1.55 (95% CI, 1.11 - 2.16); p = 0.010) and CSS (HR = 1.46 (95% CI, 1.01 - 2.10); p = 0.043) in non-metastatic GC who underwent radical surgical resection.

Comment 13: Multivariate is not a correct term in statistics. Please use “multivariable” throughout the abstract and text.

Reply: thank you for your nice comment. We replaced multivariate with multivariable and

replaced univariate with univariable (see Page 3, line 52; Page 7, line 153,155; Page 9, line 193, 195, 198; Page 10, line 205, 211, 215).

Comment 14: The authors used the laboratory data before surgery but defined overall survival and cancer-specific survival as the interval between the date of cancer diagnosis and death. This is inconsistent. Typically, overall survival and cancer-specific survival are defined as the interval between the date of surgical resection of primary tumors and patient death. Please revise.

Reply: thank you for your nice comment. We revised the definition of OS and CSS (Page 6, line 134-137). Our database office used the date of surgical resection of primary tumors as the starting point. The previous definition of OS and CSS is inappropriate.

Changes in the text: OS was defined as the period from the date of surgical resection of primary tumors to the date of death from any cause or until the last contact. CSS was defined as the period from the date of surgical resection of primary tumors to the date of death from GC.

Comment 15: The authors stated that "The cut-off point of ALI was determined by the X-tile 3.6.1 software in this cohort." This is unclear to the reader. This should be explained in details. Usually, the cut-off value for a continuous variable is determined by Youden's index. Please clarify and revise.

Reply: thank you for your suggestions. Ramp et al. first developed x-tile, a new bioinformatics tool for biomarker evaluation and outcome-based cut-point optimization [1]. After this, more and more researchers used x-tile to determine the optimal cutoff value [2-3]. Therefore, we use X-tile 3.6.1 for the cutoff of ALI. And we added a description of the process to determine the cutoff (Page 7, line 139-140).

Reference:

1. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004;10:7252–7259.

2. Li X, Lu H, Xu K, Wang H, Liang X, Hu Z. Negative lymph node count is an independent prognostic factor for patients with rectal cancer who received preoperative radiotherapy. BMC Cancer. 2017;17:227.

3. Tan Z, Zhang M, Han Q, Wen J, Luo K, Lin P, Zhang L, Yang H, Fu J. A novel blood tool of cancer prognosis in esophageal squamous cell carcinoma: the Fibrinogen/Albumin Ratio. J Cancer. 2017;8:1025–1029.

Changes in the text: With 5-year overall survival status and 5-year overall survival time as events, the optimal cut-off point of ALI was determined by the X-tile 3.6.1 software (Yale University, New Haven, CT) in this cohort

Comment 16: Statistical analysis: "Bonferroni correction was applied for post hoc analysis after Chi-squared testing." Which results were applied with Bonferroni correction? Please specify.

Reply: thank you for your comment. We rechecked our results. We used Bonferroni correction for the TNM stage and CSS in Table 1.

Comment 17: Some important factors for cancer survival are missed, including preoperative functional status (e.g., Eastern Cooperative Oncology Group Performance Status) and the American Society of Anesthesiologists physical status. Please revise.

Reply: thank you for your nice suggestion. Unfortunately, our database office did not collect these features such as Eastern Cooperative Oncology Group Performance Status) and the American Society of Anesthesiologists physical status. Therefore, we could not finish the analysis of these factors.