

Peer Review File

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Reviewer A

This study presents a novel risk score for ESCC patients undergoing chemo radiation, incorporating LDH as well as other markers. The risk score shows some ability to differentiate low, intermediate, and high-risk patients in a retrospective cohort. There are key limitations to this analysis that limit its utility.

Reply. Thank you for your feedback. We are submitting a revised manuscript to address these concerns. Detailed point-by-point responses to these concerns are provided hereunder.

Overall comments:

Comment 1. TRIPOD guidelines for a prediction model development study were not adhered to. For example, the abstract does not state that this is a single-center study.

Reply 1. We appreciate the reviewer's careful review of our manuscript. We have corrected our text as advised in the abstract and the introduction. (See Page 1, line 34; Page 4, line 14)

Comment 2. - the authors need to better support why this specific type of risk prediction tool is needed and why it is effective.

Reply 2. Considering the significant differences in prognosis among ESCC patients, it is crucial to develop a reliable and convenient prognostic tool to guide prognosis. Besides, serum LDH levels, which is easily available in routine clinical practice. Designed a risk score model for determining the prognosis of patients with ESCC who have undergone chemoradiotherapy in order to guide personalized management is urgent. (Page 4, line 11-14,20)

Introduction:

Comment 3.- The authors should be clearer about why we would expect the relationship between ESCC and LDH would be different for patients undergoing chemo radiation. Is there any evidence to suggest that LDH predicts differently based on which treatment is given? Are the patients who receive chemo radiation different from patients who receive other treatment modalities? If not, why not just rely on a more general ESCC prognosis prediction model?

Reply 3. Previous articles (14-20) have discussed the prognostic value of LDH in ESCC patients receiving different treatment methods, but draw inconsistent

conclusions. And studies regarding the influence of LDH on the prognosis have rarely examined those patients with ESCC who have undergone chemoradiotherapy. We only included this group of patients for research due to the limited studies in this area. A more general ESCC prognosis prediction model should be further studied. (Page 4, line 3-5)

Methods/Results:

Comment 4. It is not clear why the authors chose to dichotomize so many continuous variables (age, tumor length, radiation dose, CEA, cyfra21-1) for this analysis. This creates a significant amount of data loss and weakens the propensity score matching.

Reply 4. Our study focuses on different continuous variables (age, tumor length, radiation dose, CEA, cyfra21-1), with the aim of combining cut-off values to better guide patient prognosis analysis more easily and conveniently. And it is unfortunately that this inevitably leads to data loss and weakens the propensity score matching, which will be better summarized in clinical work in the future.

Comment 5. - It is not clear why the authors chose to dichotomize cT stage. This could be a categorical variable (stage 1, 2, 3, 4) that better controls for stage.

Reply 5. Due to the relatively small number of patients undergoing chemo-radiotherapy in cT1 stage and cT4 stage, we chose dichotomize cT stage.

Comment 6. - the methods do not state what variables were used to propensity-score match

Reply 6. The variables used for propensity-score match have been stated in the methods according to your kind advice. (Page 5, line 34; Page 6, line 1

Comment 7. - A calibration curve (predicted vs observed risk) should be reported to illustrate model effectiveness.

Reply 7. A calibration curve and a nomogram were reported to illustrate model effectiveness. (Page 8, line 1-7)

Discussion:

Comment 8. - a significant inverse association between LDH and survival does not necessarily "conflict" with a finding of no significant association between LDH and survival. This could simply be due to type II error, given the small sample sizes and, as the authors' mention, varying disease stage distributions within each sample.

Reply 8. We have modified our text as advised in the discussion and this shortcoming is mentioned in the article given the small sample sizes and the different disease stage distributions within each sample. (See Page 9, line 26-27)

Reviewer B

Comment 1. There have been many studies on esophageal squamous cell carcinoma. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.

Reply 1. We have modified our text as advised in the introduction. (See Page 4, line 3-5)

Comment 2. What is the greatest advantage of the risk score model in this study? What is the biggest problem we are facing? It is suggested to add relevant content to the discussion.

Reply 2. The relevant content has been added in the discussion as you suggested. (Page 9, line 31-34; Page 10, line 1-8)

Comment 3. In the introduction of the manuscript, it is necessary to clearly indicate the the relationship between serum LDH levels and the survival of patients with tumor metastasis.

Reply 3. The relationship between serum LDH levels and the survival of patients with tumor metastasis has been indicated in the introduction. (See Page 3, line 31-33)

Comment 4. The discussion section of this study is not comprehensive enough, and it is recommended to increase the biochemical correlation and therapeutic potential of lactate dehydrogenase inhibition.

Reply 4. We have modified our text as advised, and the biochemical correlation and therapeutic potential of lactate dehydrogenase inhibition has been discussed in our study. (See Page 3, line 27-33; see Page 8, line 21-24)

Comment 5. What are the methods and the practical utility for measuring both the total LDH and LDH isoenzymatic activities in the diagnosis, prognosis and prediction of cancer diseases? It is recommended to add relevant content.

Reply 5. We have modified our text as advised in the discussion. (See Page 5, line 9)

Comment 6. The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Prognostic value of lactate dehydrogenase in non-small cell lung cancer patients with brain metastases: a retrospective cohort study, J Thorac Dis, PMID: 36524070”, “Development and verification of a hypoxia-

and immune-associated prognosis signature for esophageal squamous cell carcinoma, J Gastrointest Oncol, PMID: 35557566". It is recommended to quote the articles.

Reply 6. We have modified our text as advised (see Page 4, line 9-11), "Prognostic value of lactate dehydrogenase in non-small cell lung cancer patients with brain metastases: a retrospective cohort study, J Thorac Dis, PMID: 36524070" has been cited as (12) in our study. "Development and verification of a hypoxia- and immune-associated prognosis signature for esophageal squamous cell carcinoma, J Gastrointest Oncol, PMID: 35557566" has been quoted as (21).

Comment 7. How to identify and verify the prognostic characteristics for predicting disease-free survival and overall survival of patients with esophageal squamous cell carcinoma by integrating multiple data sets? It is recommended to add relevant content.

Reply 7. A nomogram integrated the significant independent factors for predicting the survival rate was constructed. (Page 9, line 31-34; Page 10, line 1-8)

Reviewer C

1. References should be cited consecutively in text, for example, you should cite Ref.15-16 consecutively after Ref.14. Please check your paper and revise.

ESCC patients receiving surgical treatment(14, 9,20) or immunotherapy(15,16), or chemoradiotherapy but reached inconsistent conclusions (17,18), serum LDH thereby

Reply. We've checked our paper and revised according to your kind suggestions.

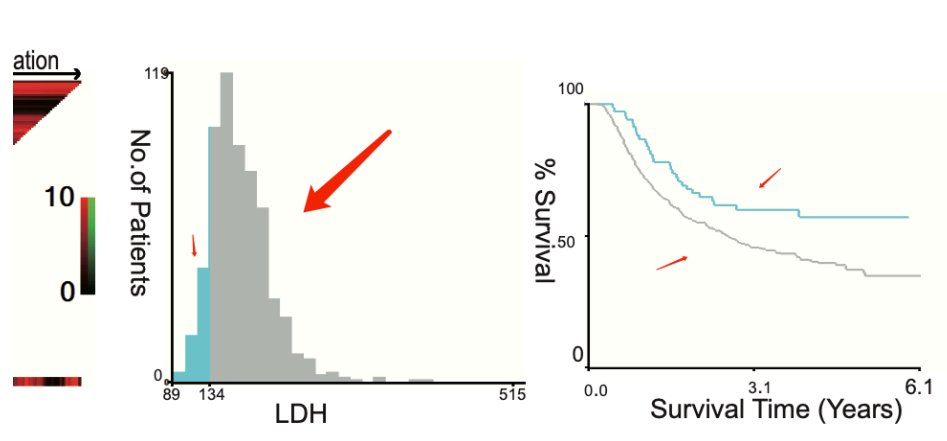
2. The reference does not match to the author's name, please check. (And you should use the last name)

predict the survival of recognize patients (9). Moreover, Luo et al. developed a prognostic risk scoring model that included the levels and neutrophil count to help verify the prognosis of patients with ESCC (14). However, no studies thus far have

Reply. The author's name has been modified as Luo HS as you suggested.

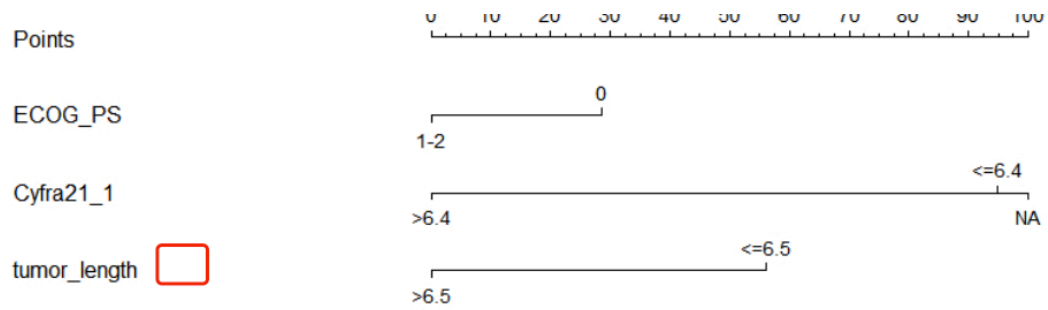
3. Figure 1:

- a. Please define the cyan and grey area in the middle image.
- b. Please define the cyan and grey lines in the last image.



Reply. The cyan and grey areas have been defined in the images.

4. Figure 5: Please indicate the unit.



Reply 4. The unit has been added according to your advice.