

Date: December 15, 2020

To: Dr. Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, Editorial Office

From: Li Dong Wang, MD, PhD, Professor and Director, State Key Laboratory of Esophageal Cancer Prevention & Treatment and Henan Key Laboratory for Esophageal Cancer Research of The First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, Henan Province, China.

Re: Point-by-point responses to the issues raised in the peer-review report(s) for the manuscript entitled as “Preoperative maximal voluntary ventilation, hemoglobin, albumin, lymphocytes and platelets predict postoperative survival in esophageal squamous cell carcinoma” (Manuscript NO.: 59936, Retrospective Study).

Dear Dr. Ma,

Many thanks for your kind email of the decision and comments for our submitted manuscript (Manuscript NO.: 59936, Retrospective Study) on December 4, 2020. Based on the comments and suggestions from the reviewers and editor for the manuscript, all the authors have read and revised the manuscript carefully. All the revisions have been marked in red color through the revised manuscript. The point by point responses are as follow.

Reviewer #1:

1. The authors stated that low FVC has been implicated as a risk prognostic factor in gastric cancer or esophageal cancer in previous studies. Please, provide difference between FVC and MVV in this cohort.

Reply: Yes. FVC has been demonstrated as a predictor in previous study. Originally, we have investigated both the FVC and MVV on the prognosis for esophageal cancer

in the present cohort. However, we didn't find any significance for the FVC on esophageal cancer. Thus, we only focused on the MVV in the present study. One possibility was that we had different source of patients, inclusion and exclusion criteria and sample size.

2. Low MVV would be correlated with morbidity or mortality due to post-operative respiratory complication. It needs to provide how the authors corrected this confounding factor.

Reply: Yes. References do report that esophageal cancer patients have a high morbidity of post-operative complications. Lagergren et al state in the review that the early postoperative complications have profound negative effects both in the short and long term (Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet 2017; 390: 2383-2396). In order to control this confounding factor, we classified the cohort into two groups (with and without complications) and used the univariate and multivariate COX proportional hazard regression model to evaluate its effect on overall survival. Finally, post-operative complication was shown as an independent risk factor for survival, which was similar to the results of previous research. After adjusting the confounding factor of post-operative complications, low MVV still remained as an independent risk factor for ESCC survival.

We have added this content to: the first, second and third paragraphs in the **RESULTS** section; the second paragraph in the **DISCUSSION** section in the revised manuscript. And the data of post-operative complications were also revised in the **Table 1, Table 2, Table 3** and the **Supplementary material 1**.

Reviewer #2:

1. Limitation of the study is to ignore completely the postoperative complication and mortality rates. As this kind of surgery has a high-morbidity, I would appreciate a split of the mortality for what concerns the complications. I assume that the lower limit of 0.19 year survival is affected by this. In my opinion as the data of pulmonary

function and nutritional status are above all linked with the incidence of complication I would say that this field should be inspected. The survival of cancer after surgery without a clear indication of what happened during and after surgery is not enough to reach good data.

Reply: Yes. As explained for the first reviewer, references do report that esophageal cancer patients have a high morbidity of post-operative complications. Lagergren et al state in the review that the early postoperative complications have profound negative effects both in the short and long term (Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet 2017; 390: 2383-2396). In order to control this confounding factor, we classified the cohort into two groups (with and without complications) and used the univariate and multivariate COX proportional hazard regression model to evaluate its effect on overall survival. Finally, post-operative complication was shown as an independent risk factor for survival, which was similar to the results of previous research. After adjusting the confounding factor of post-operative complications, low MVV, HALP score and CoMVV-HALP score still remained as independent risk factors for ESCC survival.

We have added this content to: the first, second and third paragraphs in the **RESULTS** section; the second paragraph in the **DISCUSSION** section in the revised manuscript. And the data of post-operative complications were also revised in the **Table 1, Table 2, Table 3** and the **Supplementary material 1**.

2.Type of surgery is not made explicit.

Reply: We have added the detailed surgery types for the whole cohort to the first paragraph in the **RESULTS** section in the revised manuscript.

3.The comparison of coMVV-HALP with TNM would deserve a comment in the discussion, as would a comparison between the significance of the two scores for overall and cancer specific survival.

Reply: Yes. We have made a comment for coMVV-HALP and TNM on overall survival significance in esophageal squamous cell carcinoma, which has been added

to the fourth paragraph in the **Discussion** section in the revised manuscript.

4. The abstract well represents the text and the whole study, but is a little bit. As the study is composed of different parts with lots of comparisons, I would rather just focus on main results.

Reply: We have rewritten the abstract and just focused on the main results.

5. There are a few spelling errors (e.g. in line 3 of the abstract “caners”).

Reply: We have rechecked the spelling through the manuscript.

6. Illustrations and tables. I would only add the J point on the ROC curves.

Reply: We have done as requested.

7. Discussion: as stated for pulmonary surgery cited in literature, the association of the results with the incidence of complication is not mentioned, as well as this data of postoperative mortality is not explained in the overall survival rates.

Reply: We have added the results of the association between the MVV and overall post-operative complications to the second paragraph in the **RESULTS** section in the revised manuscript. And the discussion about this has been added to the second paragraph in the **DISCUSSION** section.

Best wishes,

Yours sincerely,

Li Dong