Date: Jan. 20, 2022

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

From: Prof. Li Dong Wang (ldwangpaper2018@126.com), State Key Laboratory of Esophageal Cancer Prevention & Treatment and Henan Key Lab. For Esophageal Cancer Res, First Affiliated Hospital of Zhengzhou University, China

Re: Point by point response to the comments of "Increased prognostic value of clinical-reproductive model in Chinese female patients with esophageal squamous cell carcinoma", Manuscript NO.: 72696, Retrospective Study

Dear Dr. Ma:

Many thanks for your kind email of Jan. 09, 2022 for the decision and comments to our submitted manuscript [Manuscript NO.: 72696, Retrospective Study]. As described in main text, the present patients with esophageal squamous cell carcinoma (ESCC) were enrolled from our 500,000 esophageal and gastric cardia carcinoma databases, constructed by the cooperative team from more than 700 hospitals in China. This database has been funded by couple of major projects. The present study aims to develop and validate a clinical-reproductive model for predicting overall survival in Chinese female ESCC, and to further explore whether the model has higher prognostic value than the clinical model and TNM stage. Meanwhile, all the authors discussed extensively and agreed to the revision for the manuscript based on revision requirement and comments by reviewers from World Journal of Gastroenterology. The point by point revision of this manuscript was as follows.

Scientific quality	[　] Grade A: Excellent　[Y] Grade B: Very good　[　] Grade C: Good [　] Grade D: Fair　[　] Grade E: Do not publish
Language quality	[　] Grade A: Priority publishing　[Y] Grade B: Minor language polishing [　] Grade C: A great deal of language polishing　[　] Grade D: Rejection
Conclusion	[　] Accept (High priority)　[　] Accept (General priority) [Y] Minor revision　[　] Major revision　[　] Rejection
Re-review	[　] Yes　[Y] No

Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript is generally OK but I have some suggestions.

1. How to remove the influence of different treatment schemes before or after operation.

Reply: Thanks. In our study, treatment analysis is based on operation vs. others in the nomogram development. In cohort 1, all of 286 eligible patients which were tracked from our 500, 000 esophageal and gastric cardiac carcinoma database, constructed by the cooperative team from more than 700 hospitals in China, only 6 patients received surgery plus radiotherapy and 5 underwent surgery and chemotherapy in training cohort; and 3 patients made operation with subsequent radiotherapy and 2 patients received operation plus chemotherapy in internal validation cohort.

Several previous studies showed that surgery has been considered as the mainstay treatment for patients diagnosed with resectable ESCC. Recently, multimodal therapy that combines chemotherapy and/or radiotherapy with radical surgery has been developed. Compared with patients who received other treatments therapy (operation plus radiotherapy, operation plus chemotherapy) in our study, patients with operation showed a significant increasing OS tendency. The shorter sample size of patients with combination therapy may be one of the reasons for its negative OS influence in our study. Further related research is needed to amplify the sample size to clearly illustrate the prognostic role of treatment therapy for Chinese female patients with ESCC.

Parameters associated with $P < 0.20$ based on univariate analysis and relevant clinical factors were entered into a Cox proportional hazards regression model, which included age, incidence area, tumor differentiation, N stage, therapy, ESR1, ESR2, menarche age, menopausal age, and pregnancy number. Finally, the most suitable nomogram model was determined with the smallest

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AIC, which included incidence area, age, tumor differentiation, N stage, ESR1 expression, ESR2 expression, menopausal age, and pregnancy number. Treatment is not considered to be a potential prognostic factor in our nomogram model.

2. "Factors affecting OS in univariate analysis (P < 0.20) were included". Why select the range of P < 0.20. The corresponding reference is not proved.

Reply: Thanks. To a certain extent, the difference between the results of univariate analysis can not really reflect the effect of this factor on the final event, so we can relax the inclusion criteria of univariate analysis from P < 0.05 to P < 0.2, which can effectively avoid the omission of some important variables. Although they are not statistically significant in univariate analysis, their real effects may be underestimated or masked. After potential risk factors were selected, we performed multivariate analyses with three selection procedures (forward, backward, and stepwise) to identify the best-fit model.

3. 286 patients were randomly assigned to a primary training cohort and an internal validation cohort. It is not described the randomized manner.

Reply: Many thanks for reviewer's suggestion. We had added the description of the randomized manner in the revised section of RESULTS：In Cohort 1, all of the 286 eligible patients were randomly divided into two cohorts according by computer-generated random numbers.

PEER-REVIEW REPORT

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection

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	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In some cancers, TNM staging remains sufficient for both prognosis and treatment selection. Esophageal cancer is also in this group. This study has been a valuable study that will contribute to the literature.

Reply: Thanks. Traditionally, TNM staging by the American Joint Committee on Cancer (AJCC) is currently widely used in the clinical treatment and prognosis of cancers, including esophageal cancer. To be as a statistics-based tool to calculate the risk of clinicopathological cancer features, nomogram has been widely used in numerous fields and shown to be more accurate than the TNM staging systems for predicting prognosis. In this present study, compared with TNM staging, the full model confirmed the better discrimination for 1 year (AUC: 0.792 vs. 0.744), 3 years (AUC: 0.738 vs. 0.635), and 5 years (AUC: 0.789 vs. 0.640) OS in the primary training cohort. In the training cohort, the C-index for OS prediction was 0.701 (95% CI, 0.655-0.746), which was significantly higher than TNM staging system (0.638, 95% CI 0.576-0.699, $P = 0.013$). This superior tendency in OS prediction was also verified in the internal and external validation cohort ($P = 0.011, 0.033$). DCA for 18 months OS prediction showed that the clinical-reproductive model had a higher overall net benefit than TNM staging within a wide range of threshold probabilities. In a word, the nomogram model has increased prognostic value and can help clinicians to make individual treatment and medical decisions.

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72696

Title: Increased prognostic value of clinical–reproductive model in Chinese female patients with esophageal squamous cell carcinoma

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05560822

Position: Editorial Board

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2021-10-25

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-12-12 21:25

Reviewer performed review: 2021-12-24 14:23

Review time: 11 Days and 16 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection

Re-review	[　] Yes　[Y] No
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	Conflicts-of-Interest: [　] Yes　[Y] No

SPECIFIC COMMENTS TO AUTHORS

Good idea, well constructed work, readable well written manuscript with clear conclusion