Date: Jun. 18, 2021

To: Dr. Lian-Sheng Ma, Science Editor, 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, The First Affiliated Hospital of Zhengzhou University, China

Re: Point by point response to the comments of "Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus", Manuscript NO.: 65321, Retrospective Study

Dear Dr. Ma:

Many thanks for your kind email of Jun. 04, 2021 for the decision and comments to our submitted manuscript [Manuscript NO.: 65321, Retrospective Study]. As described in main text (page 7), the present PSEC patients 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 construct a prognostic predictive nomogram model including clinicopathological factors and neuroendocrine biomarkers for Chinese PSCE patients, and it was also determined whether the nomogram model can predict OS more accurately than the 7th TNM staging system. Importantly, all the PSCE patients were diagnosed strictly based on the PSCE criteria by WHO 2010. Meanwhile, all the authors discussed extensively and agreed to the revision for the manuscript based on revision requirement and comments by reviewers from the World Journal of Clinical Cases. All the changes had been **in red paint** through the whole manuscript. The point by point revision for the manuscript was as follows.

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 65321

Title: Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus

Reviewer's code: 05750805

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2021-03-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-08 06:38

Reviewer performed review: 2021-05-12 06:24

Review time: 3 Days and 23 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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I read with great interest the article entitled, Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus. Your data experimentally showed a nomogram model for predicting OS in Chinese patients with PSCE. The novel nomogram classified patients into different risk subgroups and showed superiority in predicting survival compared with the 7th TNM staging system. I think that the article is very interesting and useful, but I can not understand in several points and I have several questions.

(Major)

1. You compared your nomograms with the tumor node metastasis (TNM) staging system. TNM staging system is just degree of progress about esophageal cancer. You should study your nomogram by each stage.

Reply: Thanks. Indeed, nomograms can integrate and graphically display the risk factors affecting tumor prognosis, thus giving a probability value to the occurrence of clinical events, based on which decisions on individualized treatment and adjuvant therapy can be made. The result of prognostic assessment of a broad range of tumors has shown that as compared with the conventional TNM staging system, the predictive performance of nomograms is enhanced at least in terms of precision. In this study, our nomogram model had a higher overall net benefit than the 7th TNM staging system within a wide range of threshold probabilities. And then, we also conducted the 5-year overall survival prediction by the nomogram for each stage of the 7th edition TNM stages in the primary and validation cohort. The results showed that the survival rate decreased with the higher stage. We have added the description in the revised section of RESULTS (page 10; page 11; page 28, Figure 6).

2. Now a standard treatment about primary small cell carcinoma of the esophagus is chemo-radiotherapy except for stage I. Your just surgical result is very valuable for primary small cell advanced carcinoma of the esophagus. How do you think the strategy for primary small cell advanced carcinoma of the esophagus？

Reply: Thanks. At present, the role of surgery, radiotherapy, chemotherapy and other treatment methods for patients with primary small cell carcinoma of the esophagus (PSCE) at different stages is controversial due to the rarity of PSCE. Zhao et al. reported that the favorable survival trend of all treatment regimens was radiotherapy plus chemotherapy, surgery plus chemotherapy, chemotherapy alone, surgery alone, radiotherapy combined with chemotherapy in advanced PSCE patients, and the median survival time was 8.5 months. Another study conducted that radiotherapy does not improve patients' survival. Chemotherapy is still the main treatment method, and the number of chemotherapy cycles can help clinicians to judge the prognosis of patients. For patients with advanced PSCE, it is recommended to carry out comprehensive treatment based on multi-cycle chemotherapy.

In our study, all of 256 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 14 patients received surgery plus radiotherapy and 10 underwent surgery and chemotherapy in training cohort; the median survival time of 14.83 months for the former and 9.15 months for the latter. Further related studies are needed to amplify the sample size to clearly illustrate the prognostic role of treatment therapy for Chinese PSCE patients. In a word, the optimal treatment strategy for PSCE has yet to be evaluated in a large randomized controlled study, where early diagnosis and treatment can improve outcomes. In addition, PTEN deletion and PAK-1 may be potential targets for PSCE patients, and it may be possible to target PSCE in the future.

3. You showed the diagnosis of PSCE mainly depends on immunohistochemical (IHC) staining of several neuroendocrine markers, including synaptophysin (Syn), neuronal cell adhesion molecule 56 (CD56), and chromogranin A (CgA). Recently, it is common to use C-kit for evaluation of malignancy. I think it is necessary for your nomogram to evaluate c-kit. How do you think about that?

Reply: Thanks. We have re-checked the diagnosis strictly based on the PSCE diagnostic criteria by WHO 2010. The special morphological features of solid or clustered growth patterns and the positive immunostaining of neuroendocrine biomarkers contribute to the accurate diagnosis of PSCE. Indeed, the high amounts of C-kit (aka cluster of differentiation 117 [CD117], a tyrosine kinase receptor) expression in adenoid cystic carcinoma does correlate with tumor grades. More recently, C-kit associated zinc-finger transcription factor (Slug) may act as a mediator of epithelial-mesenchymal transitions and could be associated with worse TNM stage, perineural invasion, locoregional recurrence, and distant metastases.

In our study, detailed demographic, clinicopathological information, and immunostaining of 256 eligible patients were retrospectively retrieved from medical records. All patients were immunostained with CgA, Syn and CD56. Unfortunately, no C-kit immunostaining was performed. Future related study will consider the malignancy of C-KIT in cancer.

Minor

1. You showed the female to male ratio in the training and validation cohort was 1.84:1 (116/63) and 1.96:1 (51/26), respectively. Generally there are many male with esophageal cancer. Is it correct?

Reply: Thanks. We rechecked our study data carefully and replaced "female to male ratio" with "male to female ratio" in the revised manuscript (page9; page 29).

2. Would you show us the difference of small cell carcinoma and neuroendocrine tumor?

Is it same or not ?

Reply: Thanks. Neuroendocrine neoplasms (NENs) are defined as epithelial neoplasms with predominant neuroendocrine differentiation, which mainly arise from gut and bronchopulmonary systems. The 2010 World Health Organization classification for digestive system NENs have classified NENs into three categories [low-grade (G1) neuroendocrine tumor, intermediate-grade (G2) neuroendocrine tumor, and high-grade (G3) neuroendocrine carcinoma (NEC)] based on the histopathologic analysis. NEC (mainly consisting of small cell type and non-small cell type) is one kind of NENs with poor differentiation.

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 65321

Title: Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus

Reviewer's code: 05928732

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2021-03-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-08 22:52

Reviewer performed review: 2021-05-18 09:37

Review time: 9 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good
	[Y] 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)
	[ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript deals with primary small cell carcinoma of the esophagus, which is highly invasive with poor prognosis. The authors have developed a prognostic nomogram model and suggest that the indication of this new model is useful to assess the clinical outcome more accurately. This suggestion is very important in the field of treating such a serious disease, however, the manuscript has the following concerns;

Major comments

#1: Authors describes that there is no nomogram model for PSCE patients worldwide. (Page 5) However, there is already an article about nomogram for PSCE patients. (Shuai Qie et al. Medicine (Baltimore) 2021; 100:15)) The superiority of this manuscript should be considered.

Reply: Thank for reviewer's suggestion. The first nomogram, developed in 2021 by Qie S et al., was based on the public surveillance, epidemiology, and end results (SEER) database of patients in Western populations, particularly in the United States, to predict patients OS probability, without mention of Chinese population. In addition, relevant neuroendocrine markers were not

included in the mode. We have added the description in the revised section of INTRODUCTIN (page 6; page 18).

#2: In nomogram development, the treatment analysis is based on operation vs others. However, 'others' need to be classified as chemotherapy, radiation or no therapy. Combination therapy such as operation and subsequent chemotherapy should be concerned. Moreover, the usefulness of nomogram that treatment does not contribute to survival prediction is questioned. (Page 9)

Reply: Thanks. In our study, all of 256 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 14 patients received surgery plus radiotherapy and 10 underwent surgery and chemotherapy in training cohort; and 5 patients made operation with subsequent radiotherapy and 4 patients received operation plus chemotherapy in validation cohort. Several previous studies showed that operation can enhance the prognosis of some PSCE patients. Compared with patients who received other treatments therapy (operation plus radiotherapy, operation plus chemotherapy) in our study, patients with operation showed an increasing OS tendency with a median OS of 21.11 vs. 12.39 months and a 5-year OS of 28.3% vs. 15.8%, although no statistically significant. 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 PSCE patients.

Otherwise, based on the results of univariate analysis and clinical experience, histology type, gender, age, T, N, M, operation, Syn, CgA and CD56 were included in the Cox proportional hazards regression model. Finally, the most suitable nomogram model was determined using the backward step selection process with the smallest AIC, which included histology type, age, N, T, M, CgA and CD56. Therefore, treatment is not considered to be a potential prognostic factor in

our nomogram model. We have addressed these findings in the section of RESULTS, DISCUSSION, accordingly (page 9; page 13).

#3: In patients and study design, inclusion and exclusion criteria is confused. Authors are required to mention it for the readers not to misunderstand. (Page 7)

Reply: Many thanks for reviewer's suggestion. We have rechecked and modified the inclusion and exclusion criteria in the revised manuscript. A total of 256 eligible patients were finally enrolled using the following inclusion criteria: pathologically diagnosed with primary PSCE, no preoperative radiotherapy and/or chemotherapy, survival time more than 1 month, and detailed clinical baseline records. Patients with other malignant disease, or a history of anticancer treatment were excluded (page 7).

#4: Authors describe the number of patients as two-thirds and one-third. The numbers of patients are not exactly these numbers. This expression is very vague and inappropriate. (Page 9)

Reply: Thanks. We have modified the description in the revised version: 70% of the eligible patients were randomly assigned to a training cohort (n = 179) and the remaining 30% to a validation cohort (n = 77) (page 9).

Minor comments

#1 Table 1 is difficult to see. Some kind of ingenuity is needed, such as making it bold fold or adding horizontal lines.

Reply: Thanks. We have modified the Table 1 comply with you suggestions in the revised manuscript version (page 29, Table 1)

#2 Drink is misspelled on Table 1.

Reply: Thanks. We have rechecked and replaced "Drinke" into "Drink" on Table 1 in the revised manuscripts (page 29, Table 1).

#3 N is not the number of lymph nodes but the region. (Table 1, footnote)

Reply: Thanks. We have rechecked and changed "the number of lymph nodes" into "lymph node invasion" on the footnote of Table 1 in the revised manuscripts (page 3; page 5; page 30, Table 1, footnote).

#4 The gray lines are hard to see in figure 3.

Reply: Many thanks for reviewer's suggestion. We have altered the gray lines of figure 3 in the revised manuscript (page 25, Figure 3).