Reply to reviewer' comments

We thank all reviewers for their thorough reading of the manuscript and their helpful remarks that helped us to improve the manuscript (Manuscript NO: 79143 Title: Development and validation of novel nomograms to predict survival of patients with tongue squamous cell carcinoma). We have addressed the reviewer's comments as outlined below.

In addition, our revised manuscript has been polished by a professional English language editing company. And a new language certificate has been submitted on the system. We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Reviewer #1:

Comment 1: please discuss the role of PD L1 expression in this context quoting as follow:

Response 1: These have been added in paragraph 6 of the Discussion section.

Change: Second, the current model only incorporates clinicopathological parameters to predict patient outcomes, which is nonsufficient for screening patients appropriate for adjuvant therapies, especially preoperative/postoperative adjuvant immunotherapy. More molecular markers should be incorporated into the constructed model to improve its clinical application value, such as PD-1[45–47], CD47[48], CXCL11[49], and CXCR3[50], which have been reported to engage in tumor immunity and included in some efficient predictive models. (These sentences are quoted here)

Comment 2: please discuss further the limitations related to the absence of histo-pathological parameters (DOI, etc etc).

Response 2: These have been added in paragraph 6 of the Discussion section.

Change: First, the depth of invasion (DOI) has been recognized as an independent predictor of survival[8,40]. Among the tumor parameters that were significant for prognosis, such as the tumor width, area, volume, and depth, the DOI was considered the most important[41]. Additionally, extranodal extension (ENE) has been widely recognized as a significant poor prognostic factor for patients with HNSCC[42,43]. Hence, the DOI and ENE were incorporated into the T and N classification, respectively, in the AJCC 8th edition of the cancer staging manual[44]. However,

they were not available in the SEER database, thus not being included in our constructed model. Further improvements by incorporating these factors into the constructed nomogram should be undertaken in the future. (These sentences are quoted here)

Reviewer #2:

Comment 1: The external validation group has much higher C-indexes. It is not common that the model performance is way much better in external validation group than in training group, please discuss.(for CSS, for example, 0.757 vs 0.830)

Response 1: These have been added in paragraph 4 of the Discussion section.

Change: The C-index values in external validation were higher than that in the training cohort, which is consistent with that constructed by Lu and Zhang for predicting tongue cancer and low-grade endometrial stromal sarcoma, respectively[7,38]. These results may indicate the extensionality and applicability of the constructed model. (These sentences are quoted here)

Comment 2: The author should describe how the training set and (internal) validation set are assigned, rather than describe the cohort for model development and internal validation as “training cohort ” as a whole.

Response 2: The internal validation set came from the training cohort, which was assigned by the bootstrapping method when performing the internal validation. Bootstrapping refers to the use of limited sample data to rebuild new samples, which are good enough to represent the maternal sample distribution through multiple repeated sampling.

Change: Overall, 3,454 cases were selected as the training cohort for the development of new nomograms. When performing the internal validation, it was assigned by the bootstrapping method. (These have been revised in paragraph 1 of the Patient selection section.)

Comment 3: Why the T classification and surgery status are not included in the variable analysis?

Response 3: T classification was included in the variable analysis (In Tables 1, 2, and 3). Regarding surgical status: patients included in this study were all postoperative patients, that is, patients without surgery were excluded (see inclusion and exclusion criteria), so surgery status was not included in the variable.

Comment 4: In Discussion section, other studies should be included to compare with the results.

Comment 5: It is suggested that the authors should combine the literature of TSCC and make an in-depth discussion.

Response 4 and 5: A further discussion has been added in paragraph 3, 4, and 6 of the discussion section.

Change: These results indicate that the prognosis of patients with TSCC is greatly affected by the T and N stages; the more advanced the T and/or N stage, the worse the OS and CSS. (in paragraph 3). It has been demonstrated that marital status is an independent prognostic factor in patients with TSCC[9]. Married patients had better OS and CSS than unmarried patients[37], which is consistent with our findings in this study. We found the independent and significant role of marital status as a prognostic factor of patients with TSCC. In addition to the above variables, our study identified tumor site, pathology grade, and neck dissection status as independent prognostic factors of patients with TSCC. The OS and CSS of patients with TSCC are affected by these factors, which are shown in Tables 2 and 3 and Figure 2. (in paragraph 3). The C-index values in external validation were higher than that in the training cohort, which is consistent with that constructed by Lu and Zhang for predicting tongue cancer and low-grade endometrial stromal sarcoma, respectively[7,38]. These results may indicate the extensionality and applicability of the constructed model.(in paragraph 4). Due to its retrospective nature, this study has some limitations. First, the depth of invasion (DOI) has been recognized as an independent predictor of survival[8,40]. Among the tumor parameters that were significant for prognosis, such as the tumor width, area, volume, and depth, the DOI was considered the most important[41]. Additionally, extranodal extension (ENE) has been widely recognized as a significant poor prognostic factor for patients with HNSCC[42,43]. Hence, the DOI and ENE were incorporated into the T and N classification, respectively, in the

AJCC 8th edition of the cancer staging manual[44]. However, they were not available in the SEER database, thus not being included in our constructed model. Further improvements by incorporating these factors into the constructed nomogram should be undertaken in the future. Second, the current model only incorporates clinicopathological parameters to predict patient outcomes, and that more molecular markers could be incorporated to guide treatment protocols, such as PD-1[45–47], CD47[48], CXCL11[49], and CXCR3[50], which can be used to guide the screening of patients with preoperative/postoperative adjuvant immunotherapy; some articles have reported that these markers are included in the model, which works very well[50]. (in paragraph 6) (These sentences are quoted here)

Comment 6: I would like you to add to the discussion how to use the nomogram created this time effectively in clinical practice.

Response 6: The use of our nomogram has been discussed in paragraph 2 of the discussion section. (As an example, Figure 2 compares two patients with similar staging results but different treatments. The first patient was 60 years old, married, and with T2 and N1 stage cancer on the anterior 2/3 of the tongue that exhibited moderate differentiation; that patient underwent neck dissection and received postoperative chemotherapy. The second patient was 70 years old, unmarried, and with T2 and N1 stage cancer on the anterior 2/3 of the tongue that exhibited high differentiation; that patient underwent neck dissection but did not receive radiation treatment. According to the conventional TNM staging system, both patients had the same TNM stage and therefore should have similar OS. However, our nomograms predicted that the respective 3- and 5-year OS were 64% and 55% for the first patient, whereas they were 43% and 33% for the second patient. “These sentences are quoted here”)

Comment 7: Not enough novel.

Response 7: Although several researchers have reported on the prognosis of patients with TSCC based on demographic and histopathological variables, they used only one database—both for model development and model validation. However, we used two databases, one for model development and the other for external validation. Externally validated models are more convincing than internally validated. What’s

more, they only evaluated the discrimination and accuracy of the model, but ignoring clinical utility of them. Clinical utility refers to whether the constructed models facilitate decision-making and thus improve patient outcomes. It is also an indispensable part of the application of the model in clinical practice. In this study, we evaluated not only the discrimination and accuracy of the model, but also its clinical utility.

References involved in this letter:

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