PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic prediction models for oropharyngeal squamous cell carcinoma (OPSCC): a protocol for systematic review, critical appraisal and meta-analysis
AUTHORS	Lu, Zhen; Zhou, Xinyi; Fu, Leiwen; Li, Yuwei; Tian, Tian; Liu, Qi; Zou, Huachun

VERSION 1 – REVIEW

REVIEWER	Caldeira, Patricia UFMG
REVIEW RETURNED	20-Apr-2023

GENERAL COMMENTS	1- For a systematic review, searching two bases only seems to be insufficient. Why the authors did not include other databases like Web of Science, Cochrane, etc? 2- In the introduction, authors stressed out the HPV association with OPSCC, which is correct. However, I failed to find any mention about the HPV status in the methods: your systematic review is about HPV-related OPSCC or HPV-unrelated OPSCC? This should be clearly stated, as HPV-related tumors are known to have a better prognosis than the HPV-unrelated ones. Indeed, the last AJCC classification consider these as distinct entities. 3- Professional english review will improve the manuscript. 4- The dates of the study should be included in the manuscript.

REVIEWER	Cheng, Bo Zhongnan Hospital of Wuhan University
REVIEW RETURNED	02-Jun-2023

GENERAL COMMENTS	Manuscript:“ Prognostic prediction models for oropharyngeal squamous cell carcinoma (OPSCC): a protocol for systematic review, critical appraisal, and meta-analysis”, by Lu, et al. Thanks for giving me the opportunity to review this study. 1. In general, it is believed that the publication of the protocol can fill the gap of lack of high-quality research in the field, and establish research design guidelines. We found that relevant systematic reviews of predictive models have been published in other diseases, there is no significant innovation in the design of this study. 2. The author introduces the content related to HPV-positive OPSCC in the background, but there is no relevant involvement in the subsequent experimental design. 3. The data processing method should be more specific, describing the method of visualizing and visually displaying individual research results and merged results, and explaining the

	heterogeneity testing methods and analysis software of meta-analysis. 4. OPSCC in the author's title is limited to squamous cell carcinoma and in the search formula, other types of cancer were not excluded.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Patricia Caldeira, UFMG

Comments to the Author:

1- For a systematic review, searching two bases only seems to be insufficient. Why the authors did not include other databases like Web of Science, Cochrane, etc?

Response:

Based on the comment, we have now enlarged our searching electronic databases, which include MEDLINE, Embase, Web of Science, the Cochrane Library and China National Knowledge Infrastructure (CNKI).

2- In the introduction, authors stressed out the HPV association with OPSCC, which is correct. However, I failed to find any mention about the HPV status in the methods: your systematic review is about HPV-related OPSCC or HPV-unrelated OPSCC? This should be clearly stated, as HPV-related tumors are known to have a better prognosis than the HPV-unrelated ones. Indeed, the last AJCC classification consider these as distinct entities.

Response:

We apologize for the lack of clarity. This study will include both HPV-positive and HPV-negative OPSCC. We have now added this information on the scope of this study to the Methods section.

Line 163-164: In addition, this study will include both HPV-positive and HPV-negative OPSCC.

3- Professional english review will improve the manuscript.

Response:

We apologize for any shortcomings in our English writing. The revised manuscript has now been reviewed by a native English speaker.

4- The dates of the study should be included in the manuscript.

Response:

We have now included the planned start and end dates for the study in the Methods section of the revised manuscript.

Line 139-141: Formal activities for this study are scheduled to commence in September 2023 and should conclude by June 2026. Data analysis and dissemination of results will be completed in this period.

Reviewer: 2

Dr. Bo Cheng, Zhongnan Hospital of Wuhan University

Comments to the Author:

Manuscript:“ Prognostic prediction models for oropharyngeal squamous cell carcinoma (OPSCC): a protocol for systematic review, critical appraisal, and meta-analysis”, by Lu, et al. Thanks for giving me the opportunity to review this study.
1. In general, it is believed that the publication of the protocol can fill the gap of lack of high-quality research in the field, and establish research design guidelines.
We found that relevant systematic reviews of predictive models have been published in other diseases, there is no significant innovation in the design of this study.

Response:

Thank you for your comment. We also noted that researchers have been focusing efforts on relevant systematic reviews of predictive models for other diseases, while rare systematic reviews of predictive models for OPSCC have been published so far. This work will assess prognostic prediction models for OPSCC and lay a foundation for future research programs to develop and validate evidence-based prognostic prediction models for OPSCC. This will support risk-differentiated clinical decision making at various health service levels, ultimately, facilitate more personalized management of OPSCC and positively enhance the quality of life of patients. We think these contribute to the innovation in the design of this study, and the work may attract broad interdisciplinary interest.

2. The author introduces the content related to HPV-positive OPSCC in the background, but there is no relevant involvement in the subsequent experimental design.

Response:

We apologize for the lack of clarity. HPV is known to be the most significant factor for OPSCC, which results in essential consideration about the infection with HPV in almost all the predictive modelling studies for OPSCC. This study will systematically review published prognostic prediction models for survival outcomes in patients with OPSCC, which includes both HPV-positive and HPV-negative OPSCC. We have now added this information on the scope of this study to the Methods section.

Line 163-164: In addition, this study will include both HPV-positive and HPV-negative OPSCC.

3. The data processing method should be more specific, describing the method of visualizing and visually displaying individual research results and merged results, and explaining the heterogeneity testing methods and analysis software of meta-analysis.

Response:

We have now expanded the data processing methods in the Methods section of the revised manuscript.

Line 290-295: The characteristics of models will be tabulated to show classification measures such as sensitivity, specificity, area under the receiver operating characteristic curve (AUROC)[1], where reported. Relevant analyses and visualizing will be performed using R software version 4.2.1 (R Core Team, Vienna, Austria, available at: https://www.R-project.org).

Line 312-316: Where meta-analysis is feasible, performance measures such as discrimination (e.g., area under the receiver operating characteristic curve) and calibration (e.g., calibration slope) will be pooled and analyzed using a random-effects model[2], which provide estimates of the average performance of predictive models across the selected modelling studies.

Line 321-328: The I^2 test is a statistical measure used in systematic reviews and meta-analyses to assess heterogeneity among studies included in the analysis. It quantifies the proportion of total variation in effect estimates that is due to heterogeneity rather than chance. It is expressed as a percentage and ranges from 0% to 100%. A higher value of I^2 suggests a greater degree of heterogeneity. Potential sources of heterogeneity will be investigated by undertaking a meta-regression analysis. The analysis will be carried out using R software version 4.2.1 (R Core Team, Vienna, Austria, available at: https://www.R-project.org).

4. OPSCC in the author's title is limited to squamous cell carcinoma and in the search formula, other types of cancer were not excluded.

Response:

We deigned the draft search strategy based on systematic reviews of treatments for OPSCC[3-6] and related publications[7], to ensure highly sensitive. The reference lists of included model development studies and relevant systematic reviews for further studies will be hand searched for additional potentially relevant citations. We aimed to avoid missing any valuable relevant predictive modelling studies for OPSCC. We have now reported the reason of the search strategy being highly sensitive in the revised manuscript.

Line 223-224: We aimed to avoid missing any valuable relevant predictive modelling studies for OPSCC.

Reference

1. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014;11(10):e1001744. doi: 10.1371/journal.pmed.1001744 [published Online First: 20141014]
2. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions [Available from: https://training.cochrane.org/handbook/current accessed 3 February 2023.
3. Parmar A, Macluskey M, Mc Goldrick N, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. *Cochrane Database of Systematic Reviews* 2021(12) doi: 10.1002/14651858.CD006386.pub4
4. Howard J, Dwivedi RC, Masterson L, et al. De-intensified adjuvant (chemo)radiotherapy versus standard adjuvant chemoradiotherapy post transoral minimally invasive surgery for resectable HPV-positive oropharyngeal carcinoma. *Cochrane Database of Systematic Reviews* 2018(12) doi: 10.1002/14651858.CD012939.pub2
5. Perry A, Lee SH, Cotton S, et al. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. *Cochrane Database of Systematic Reviews* 2016(8) doi: 10.1002/14651858.CD011112.pub2
6. Chan KKW, Glenny AM, Weldon JC, et al. Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy. *Cochrane Database of Systematic Reviews* 2015(12) doi: 10.1002/14651858.CD010341.pub2
7. Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *New England Journal of Medicine* 2010;363(1):24-35. doi: 10.1056/NEJMoa0912217