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Prognostic prediction models for oropharyngeal squamous cell carcinoma (OPSCC): a protocol for systematic review, critical appraisal and meta-analysis

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25 Abstract

Background: Oropharyngeal squamous cell carcinoma (OPSCC) is increasingly prevalent and has significantly heterogeneous risks of survival for diagnosed individuals due to the inter-related risk factors. Precise prediction of the risk of survival for an individual patient with OPSCC presents a useful adjunct to therapeutic decision making regarding the management of OPSCC. This study will systematically review published prognostic prediction models for survival outcomes in patients with OPSCC, describe their characteristics, compare performance, and assess risk of bias and real-world clinical utility.

Methods: Studies will be identified by searching MEDLINE and Embase databases. Selection of eligible studies, data extraction, and critical appraisal will be conducted independently by two reviewers. Included studies will be systematically summarized using appropriate tools designed for prognostic prediction modelling studies. Performance measures of these models will be pooled and analyzed with meta-analyses if feasible.

40 Discussion: This work will lay a foundation for future research programs to develop, 41 validate, and assess prognostic prediction models for OPSCC. The final model will 42 estimate the absolute risk of survival for patients with OPSCC and can be implemented 43 into real-world clinical practice as an evidence-based prognostic prediction model for 44 OPSCC. This work will support risk-differentiated clinical decision making at various 45 health service levels, ultimately, facilitate more personalized management of OPSCC 46 and positively enhance the quality of life of patients.

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Systematic review registration: PROSPERO registration number CRD42023400272.

Keywords: Oropharyngeal squamous cell carcinoma (OPSCC); Prognostic prediction

model; Survival; Systematic review; Head and neck carcinoma

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54 Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is one of the head and neck carcinomas, which originates in tissues of the oropharynx (the part of the throat at the back of the mouth, including the soft palate, the base of the tongue, and the tonsils)^[1-3]. OPSCC represents an increasingly prominent public health concern internationally. Albeit OPSCC only represents 0.9% of all cancers, its incidence has been rapidly growing worldwide in recent years, with an estimated 182666 new cases in 2020^[4-6]. An increased incidence of OPSCC among men under 45 years of age has been reported recently^[6-9]. Moreover, the death rate of OPSCC is rising by 2% worldwide per year, compared with other head and neck carcinomas^[10], with an estimated 86742 new deaths in 2020^[4]. Of note, OPSCC has a special feature of epidemiologic trends in different settings worldwide. Over the past few decades, OPSCC diagnosis increased especially in developed countries, including the United States, and Canada^[6, 11-13], while South-central Asia had the highest proportion of new OPSCC cases (35.1% of global incident cases)^[14]. Across China, there has also been an obvious increase in OPSCC in the recent decade, especially for incidence and mortality of males and in rural areas, whereas the rates of females remained stable^[15].

Compared with other common type of head and neck carcinomas, OPSCC is likely to be advanced (i.e., with neck metastases) at the time point of diagnosis and its primary treatment is more likely to be aggressive (such as radiation therapy and/or chemoradiation), which may have devastating effects on the survival of these patients^[16-19]. OPSCC is a heterogeneous condition with inter-related factors Page 5 of 26

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significantly modifying the absolute risk of survival at an individual level.

Human papillomavirus (HPV) is considered to be the most significant risk factor for OPSCC^[20-22]. HPV is a major carcinogen, which meets the epidemiological criteria for OPSCC causality^[23, 24]. Up to 70 % of newly diagnosed OPSCCs are HPV positive^[25]. In addition, the current identified risk factors include heavy smoking and alcohol consumption^[26]. However, it is worth noting that HPV-positive OPSCC patients are usually confronted with decades of significantly improved quality of life, compared to the HPV-negative OPSCC group of patients^[19]. HPV-positive OPSCC is associated with a 58% reduction in the risk of death compared to its $counterpart^{[27]}$. In contemporary real-world clinical practice, interventions (treatment and/or management) are implemented after diagnosis of OPSCC, without individualized risk assessment of the absolute risk of survival. Consequently, in case of immediate start of treatment after diagnosis of OPSCC, this mode of intervention fails to identify of the proportion of patients at high risk (with a lower probability to obtain a good response) who should have received new or more aggressive therapy regimens. Meanwhile, patients at low risk will not be spared from harm of unnecessary aggressive cancer treatment and significant financial burden of cancer management. Therefore, limitations of the one-size-fits-all mode of intervention and lack of risk-differentiated decision making are evident. In this regard, it is imperative to develop a precise and applicable prognostic prediction model for calculating the absolute risk of survival for patients with OPSCC, based on considering any relevant risk factors related to survival and individual demographical characteristics. Accurate prediction of risk of survival

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would then guide risk-differentiated clinical decision making at health services level,
ultimately, facilitate more personalized management of OPSCC and positively enhance
the quality of life of patients.

This systematic review will identify, screen, and assess all published prognostic prediction modelling studies for survival outcomes in patients with OPSCC. We aim to answer the question: what prognostic prediction models have been developed and validated for application in patients with OPSCC to predict risk of survival and inform clinicians' therapeutic decision making regarding the management of OPSCC. The detailed objectives of this systematic review are: 1. To systematically identify existing prognostic prediction models for survival outcomes in patients with OPSCC; 2. To qualitatively describe characteristics of identified models; 3. To quantitatively compare their performance across different clinical settings and population from different regions in the world with meta-analysis where appropriate; 4. To rigorously assess the conduct and real-world clinical utility of these prognostic prediction modelling studies.

113 Methods

This systematic review protocol was registered on the PROSPERO international registry of systematic reviews on February 27, 2023 (CRD42023400272). This protocol for the systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline^[28], Cochrane Prognosis Methods Group Protocol Template^[29], ransparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)

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statement^[30], PROBAST tool (prediction model risk of bias assessment)^[31], and the
corresponding CHARMS checklist (checklist for critical Appraisal and data extraction
for systematic reviews of prediction modelling studies)^[32].

A systematic review of prognostic prediction modelling studies for survival outcomes in patients with OPSCC will be conducted to identify eligible studies published before March 2023. The review will be guided by the recommendations of The PROGnosis RESearch Strategy (PROGRESS) Partnership, which is international. an interdisciplinary collaboration that has published a framework to improve the standards of prognosis research to improve its translational impact. The framing of the review question is presented in Table 1.

Table 1 Framing of this systematic review with key items identified by the CHARMS checklist^[32]

Items Comments 1. Prognostic versus diagnostic Prognostic prediction model (Aimed to predict future survival outcomes prediction model of people diagnosed with OPSCC) Prognostic prediction models to inform clinicians' therapeutic decision 2. Intended scope of the review making regarding the management of OPSCC All study types including prognostic prediction modelling studies (with 3. Type of prediction modelling studies or without external validation) and external model validation studies (with or without model updating) 4. Target population to whom the Patients diagnosed with OPSCC according to criteria in each eligible prediction model applies study included in the review 5. Outcome to be predicted Future survival outcomes after diagnosis of OPSCC, including overall survival (and/or disease-related mortality), progression-free survival, and disease-free survival Survival outcomes occurring at any time point after diagnosis of OPSCC 6. Time span of prediction 7. Intended moment of using the At any time point after diagnosis of OPSCC model

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136 Eligibility criteria

Notes: OPSCC, oropharyngeal squamous cell carcinoma.

137 Table 2 shows the review question in population, index, comparator, outcome, timing,

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setting, and study type (PICOTS) format^[33]. Selection of studies will be based on the
eligibility criteria framed with the PICOTS system, which is a modification of the
established PICO system and designed for the specific requirements of systematic
reviews of prediction models with additional consideration for timing and clinical
setting^[31].

144 Table 2 Eligibility criteria for the systematic review framed with the PICOTS system^[33]

Items	Inclusion criteria	Exclusion criteria
Population	Patients diagnosed with OPSCC according to criteria	
	in each eligible study included in the review	
Index	Development or external validation of a prognostic	Diagnostic prediction models
	prediction model for survival outcomes in patients	(e.g., diagnostic prediction
	with OPSCC (e.g., prognostic prediction models for	models for diagnosis of
	patients with OPSCC to predict survival outcomes)	OPSCC)
Comparator	No predefined comparator	
Outcomes (primary)	Overall survival (and/or disease-related mortality, if	
	possible)	
Outcomes (secondary)	Progression-free survival, and disease-free survival	
Timing	Survival outcomes occurring at any time point after	
	diagnosis of OPSCC	
Setting	Prognostic prediction models that are designed to be	
	used by healthcare professionals in the clinical setting	
	to inform their therapeutic decision making regarding	
	the management of OPSCC, at any time point after	
	diagnosis of OPSCC	
Study type	Any study design including primary research (e.g.,	Editorial comments or letters
	randomized controlled trial, cohort study, case-control	
	study) or secondary research (e.g., systematic review)	
	that reports on one or more statistical models, tools or	
	scores with at least two predictors proposed to predict	
	an individual's risk of a future survival outcome	
	(prognostic prediction modelling studies). Prognostic	
	prediction modelling studies can be either model	
	development, model validation or a combination	

¹⁴⁶ Notes: OPSCC, oropharyngeal squamous cell carcinoma.

Population

150 Studies reporting on prognostic prediction models proposed for survival outcomes in

151 patients with OPSCC will be included into the systematic review. OPSCC could have

been diagnosed according to criteria in each eligible study included in the review.

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154	Intervention
155	Prognostic prediction modelling studies (with or without external validation) and
156	external model validation studies (with or without model updating) will be considered
157	for inclusion into the systematic review, if they were intended to inform clinicians'
158	therapeutic decision making regarding the management of OPSCC.
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160	Outcome
161	The included outcome endpoints related to OPSCC, defined as the outcomes of interest
162	in the eligibility criteria, are aligned with those agreed by consensus of systematic
163	reviews for treatment of OPSCC and draw on published search strategies for similar
164	review questions for prognostic models of cancers ^[16, 17, 27, 34-38] .
165	The primary outcome endpoint is overall survival (OS). We choose this endpoint
166	because it has the greatest clinical relevance and is most important for patients
167	diagnosed with OPSCC. Furthermore, OS is an objective endpoint not susceptible to
168	bias of the outcome assessor. In addition, disease-related mortality will be considered
169	if possible. The secondary outcome endpoints include progression-free survival (PFS)
170	and disease-free survival (DFS). We choose these endpoints as patients with similar
171	survival may nevertheless have different lengths of time without disease progression or
172	symptoms, depending on both initial treatment after diagnosis and disease
173	characteristics.
174	Outcome endpoints will be assessed in hierarchical fashion in the following order: OS

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(and/or disease-related mortality), PFS, and DFS. The timing and effect measures for
each outcome endpoint will be as defined according to each eligible study included in
the review. In addition, we will not require studies to have a minimum follow-up
duration for inclusion in this systematic review.

- 179
- 180 Timing

181 Each eligible study included in the review should report on prognostic prediction182 models for survival outcomes occurring at any time point after diagnosis of OPSCC.

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184 Setting

Prognostic prediction models that are designed to be used by healthcare professionals
in the clinical setting, at any time point after diagnosis of OPSCC, will be considered
for inclusion in the review.

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Type of studies and limits

Any study design including primary research (e.g., randomized controlled trial, cohort study, case-control study) or secondary research (e.g., systematic review) that reports on one or more statistical models, tools or scores with at least two predictors proposed to predict an individual's risk of a future survival outcome (prognostic prediction modelling studies) will be considered for inclusion in the review. Prognostic prediction modelling studies can be either model development, model validation or a combination. Specifically, editorial comments or letters will be excluded from the review. Eligible

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studies included in the review will be limited to those conducted in humans by applying
The Cochrane Group's filter for Humans not Animals filter^[39].

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200 Search methods for identification of studies

201 Databases

The following electronic databases will be systematically searched to identify eligible studies from their inception: 1) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily on Ovid and Ovid MEDLINE(R) (from 1946 to present); 2) Embase Classic+Embase on Ovid (from 1947 to present).

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208 Search strategy

A highly sensitive search strategy, based on the eligibility criteria for the systematic review and combining subject indexing terms (i.e., MeSH) and free-text search terms, will be designed for MEDLINE Ovid. The search strategy, specifically, subject indexing terms will be translated appropriately for Embase.

The draft search strategy will combine concepts related to prognostic prediction modelling studies, OPSCC, and survival outcomes. The updated version of a validated filter for prediction modelling studies^[40] will be used. For OPSCC and survival outcomes related to OPSCC, a search strategy aligned with those agreed by consensus of peer-reviewed systematic reviews of treatments for OPSCC and drew on published search strategies for similar review questions for prognostic models of cancers will be

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used^[16, 17, 27, 34-38]. The draft search strategy is provided in Supplementary Table 1. The
final search strategy will be iteratively refined.

The reference lists of included model development studies and relevant systematic reviews for further studies will be hand searched for additional potentially relevant citations. The included studies will be checked for error or fraud. We will not place any restrictions on language, publication year or publication status when searching the electronic databases. Any non-English studies identified will be translated and assessed for eligibility.

Data collection and analysis

229 Selection process

Two independent reviewers will screen and assess the abstracts of each study identified by the final search strategy. Duplicate records will be excluded using a systematic, rigorous and reproducible method utilizing a sequential combination of fields including author, year, title, journal and pages^[41]. Thereafter, if the information suggests that the study meets the eligibility criteria for the review (Table 2) or there is any doubt against eligibility, full texts of the studies will be independently accessed for further assessment. Any conflict will be resolved through discussion with a senior advisor (HZ), where required.

239 Data extraction

240 Two independent reviewers will extract data from eligible studies included in the

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review, using a standardized electronic form developed with reference to the checklist
for critical Appraisal and data extraction for systematic Reviews of prediction
Modelling Studies (CHARMS)^[32].

For each eligible study, we plan to seek information on objective, source of data, participants, survival outcome(s) to be predicted, candidate predictors, sample size, missing data, model development, model performance (discrimination, calibration, clinical utility, and measures of case-mix variation), results including final multivariable models and interpretation of presented models, and model validation^[32]. Moreover, information on diagnostic criteria for OPSCC and treatment type after diagnosis will also be extracted. Missing data will be obtained from the study authors wherever possible, in addition, if insufficient information is obtained the study will be excluded from the review. Any disagreement will be resolved through consultation with a senior advisor (HZ), when necessary.

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255 Data management

Covidence systematic review software will be used to manage screened records
throughout the review (Veritas Health Innovation, Melbourne, Australia. Available at:
<u>http://www.covidence.org</u>). Eligible studies included in the review will be imported
into Endnote reference manager software (Version 20.4.1, Clarivate Analytics,
Philadelphia, USA. Available at: <u>https://endnote.com/</u>).

262 Critical appraisal

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The methodological quality (risk of bias) and relevance (applicability) to the review question (Table 1 and 2) of eligible studies included in the review will be systematically assessed using the prediction model risk of bias assessment tool (PROBAST)^[31]. This tool is structured around four key domains (participants, predictors, outcome, and analysis), of which each will be rated as high, low, or unclear risk of bias. Two independent reviewers will assess the risk of bias and applicability of each eligible study included in the review. Each study will be given a rating of high, low, or unclear risk for each of the four domains. Any disagreement will be resolved through discussion and consultation with a senior advisor (HZ) to reach a consensus, where required. Qualitative data synthesis of prognostic prediction models All extracted data on prognostic prediction models from included studies will be tabulated to facilitate comparison of survival outcomes to be predicted, predictors included in the final model and performance measures^[32]. Measures of uncertainty will be reported when published or approximated using published methods^[33]. Quantitative analysis and comparison of the predictive performance of prognostic prediction models Our quantitative analysis will depend on the data available, the final number of eligible prognostic prediction models included in the review, and the type of prognostic prediction modelling studies (i.e., development or validation).

284 We will attempt a meta-analysis by type of prognostic prediction modelling studies, if

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included studies are sufficiently homogenous. Clinical homogeneity will be regarded
as satisfied, if the review identifies: 1) multiple validation studies for a common
prognostic prediction model are identified or, 2) multiple development studies where
the target population to whom the model applies, and survival outcomes to be predicted
are considered similar or the same.

291 Meta-analysis and investigation of heterogeneity

Where data permits, meta-analysis will be conducted with reference to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group guidelines^[42]. 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^[39]. The restricted maximum likelihood and Hartung-Knapp-Sidik-Jonkman methods will be used to estimate the between-study heterogeneity and 95% confidence intervals for the average performance^[33]. Statistical or clinical homogeneity will be assessed using the I^2 test, where an I^2 value > 50% indicates moderate to high heterogeneity, as specified in published literatures^[39, 43]. Potential sources of heterogeneity will be investigated by undertaking a meta-regression analysis.

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304 Subgroup analysis

305 Where there are enough eligible studies included in the review, we planned to conduct 306 subgroup analyses. Subgroup analyses will be undertaken according to the type of **BMJ** Open

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prognostic prediction modelling studies (i.e., development or validation), target
population to whom the model applies, diagnostic criteria for OPSCC, whether
population was treated (yes/no), treatment type after diagnosis, the follow-up duration,
survival outcomes to be predicted, and study quality (risk of bias).

312 Sensitivity analysis

If meta-analysis would be performed, we would undertake sensitivity analyses to explore the influence on effect size for exclusion of studies at lower and higher risk of bias^[33].

317 Summary of findings

Reporting and presentation of findings will be guided by the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses)^[28], and relevant recommendations from the TRIPOD statement (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis)^[30]. The GRADE approach (grading of recommendations, assessment, development and evaluation) will be utilized to determine confidence in estimates^[44, 45].

Discussion

This systematic review will identify, screen, and assess all published prognostic prediction models for survival outcomes in patients with OPSCC. All eligible models included in the review will be systematically summarized and compared for their

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performance across different clinical settings and population from different regions inthe world with meta-analysis if feasible.

A prognostic prediction model for survival outcomes in patients with OPSCC is designed to be used by healthcare professionals in the clinical setting to inform their therapeutic decision making regarding the management of OPSCC, at any time point after diagnosis of OPSCC. Compared with other common types of head and neck carcinomas, OPSCC is likely to be advanced (i.e., with neck metastases) at the time point of diagnosis and its primary treatment is more likely to be aggressive (such as radiation therapy and/or chemoradiation), which may have devastating effects on the survival of these patients^[16-19]. Survival outcomes affecting the quality of life of these patients are of utmost importance. Hence, accurate prediction of risk of survival would guide risk-differentiated clinical decision making at health services level, ultimately, facilitate more personalized management of OPSCC and positively enhance the quality of life of patients. Consequently, in case of immediate start of treatment after diagnosis of OPSCC, identification of patients with a lower probability to obtain a good response will aid in making decisions regarding management, for instance, deciding new or more aggressive therapy regimens would be delivered to this proportion of patients at high risk. In contrast, in case of a watch-and-wait strategy, differences in estimated prognostic survival risks can affect patient management regarding surveillance and treatment.

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349 Prognosis-related research in OPSCC has been seeking to predict risk of survival after350 diagnosis based on routinely collected data, with a view to directing treatment and/or

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> management efforts in real-world clinical practice. This systematic review will make an important contribution to the understanding of risk of survival for patients diagnosed with OPSCC. Moreover, each eligible prognostic prediction models included will be compared head-to-head for their performance and clinical utility in the review. From this perspective, the review will comprehensively promote the consideration of risk-differentiated clinical management of OPSCC in real-world practice. Furthermore, in case that insufficient applicable models are identified, or screened models have poor performance, and/or high risk of bias, we will provide explicit rationale and detailed guidance for development, validation, and/or updating for prognostic prediction models for OPSCC. In contrast, in case that high-performance models are identified, they will be valuable to helping clinicians and patients with OPSCC understand and consider estimated risk of survival in shared decision making, objectively and systematically. As such, this systematic review forms the foundations of future research programs to develop, validate, and assess a prognostic prediction model for OPSCC across the four themes of the PROGRESS prognosis research framework^[46]. We noted that researchers have been focusing efforts on developing new prognostic prediction models to date, however, disproportionate efforts have been put into improving and ultimately implementing existing models into real-world clinical practice, which have caused a huge waste of research resources. Therefore, we strongly recommend that, in the future, researchers could optimally utilize information from our review. If appropriate, seeking to validate and update existing prognostic prediction models would be better choice^[47]. In conclusion, this systematic review will comprehensively consider contemporary best

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4	373	practice and evidence of prognostic prediction modelling studies for OPSCC. This work
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7	374	will support risk-differentiated clinical decision making at health services level,
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9	375	ultimately, facilitate more personalized management of OPSCC and positively enhance
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12	376	the quality of life of patients.
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25	381	funding parties did not have any role in the design of the study or in the explanation of
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27	387	the data ZI and HZ conceived the study and designed the protocol ZI XZ LE VI
28	302	the data. ZE and The concerved the study and designed the protocol. ZE, XE, EI, TE,
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30	383	TT, and QL contributed to the manuscript with all authors critically revising the
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33	384	manuscript. All authors have read and approved the final version of the manuscript.
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38	386	Conflicts of interest
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3 4	390	Refer	ences
5	201	1	Shibabara T. [Oral cancer, diagnosis and therapy, I. Clin Calcium, 2017, 27 (10), p. 1427, 1422
6 7	202	1.	Sinbanara, 1., [Ordi cuncer-diagnosis una therapy]. Clin Calcium, 2017. 27(10): p. 1427-1433.
8	392	2.	Gool, Z., J.Y. Chan, and C. Fakhry, The epidemiology of the human papiliomavirus related to
9	393		oropharyngeal head and neck cancer. Laryngoscope, 2016. 126 (4): p. 894-900.
10	394	3.	Definition of Oropharyngeal Cancer—NCI Dictionary of Cancer Terms—National Cancer
11	395		Institute. Available from: <u>https://www.cancer.gov/publications/dictionaries/cancer-</u>
12	396		terms/def/oropharyngeal-cancer.
14	397	4.	Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality
15	398		Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. 71(3): p. 209-249.
16 17	399	5.	De Felice, F., et al., Advances in the Management of HPV-Related Oropharyngeal Cancer. J
17	400		Oncol, 2019. 2019 : p. 9173729.
19	401	6.	Chaturvedi, A.K., et al., Worldwide trends in incidence rates for oral cavity and oropharyngeal
20	402		<i>cancers</i> . J Clin Oncol, 2013. 31 (36): p. 4550-9.
21	403	7.	Abram, M.H., et al., Epidemiology of oral squamous cell carcinoma. SADJ, 2012. 67(10): p. 550-
22	404		3.
24	405	8.	Maichrzak, E., et al., Oral cavity and oropharynaeal squamous cell carcinoma in young adults:
25	406	0.	a review of the literature Badiol Oncol 2014 48 (1): p 1-10
26	407	٥	Auluck A et al. Reputation-based incidence trends of oronharungeal and oral cavity cancers
27	407	5.	hu say among the paperest and undergrivilaged populations. PMC Capeer, 2014, 14(1): p. 216
29	408	10	by sex among the poolest and underprivileged populations. Bive Cancer, 2014. 14(1), p. 516.
30	409	10.	Lee, S.C., et al., Fluid Biomarkers in HPV and Non-HPV Related Oropharyngeal Carcinomas:
31	410		From Diagnosis and Monitoring to Prognostication-A Systematic Review. Int J Moi Sci, 2022.
32	411		23 (22).
34	412	11.	Simard, E.P., L.A. Torre, and A. Jemal, International trends in head and neck cancer incidence
35	413		rates: differences by country, sex and anatomic site. Oral Oncol, 2014. 50 (5): p. 387-403.
36	414	12.	Chi, A.C., T.A. Day, and B.W. Neville, Oral cavity and oropharyngeal squamous cell carcinoma-
37	415		<i>-an update</i> . CA Cancer J Clin, 2015. 65 (5): p. 401-21.
30 39	416	13.	Lambert, R., et al., Epidemiology of cancer from the oral cavity and oropharynx. Eur J
40	417		Gastroenterol Hepatol, 2011. 23(8): p. 633-41.
41	418	14.	Shield, K.D., et al., The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in
42	419		2012. CA Cancer J Clin, 2017. 67 (1): p. 51-64.
43 44	420	15.	Liu, J., et al., Incidence, mortality, and temporal patterns of oropharyngeal cancer in China: a
45	421		population-based study. Cancer Commun (Lond), 2018. 38 (1): p. 75.
46	422	16.	Parmar, A., et al., Interventions for the treatment of oral cavity and oropharyngeal cancer:
47	423		chemotherapy. Cochrane Database of Systematic Reviews, 2021(12).
48 49	424	17.	Howard, J., et al., De - intensified adjuvant (chemo)radiotherapy versus standard adjuvant
50	425		chemoradiotherapy post transoral minimally invasive surgery for resectable HPV - positive
51	426		oronharvngegi carcinoma. Cochrane Database of Systematic Reviews. 2018(12)
52	420	10	Howbroe Michaelsen S., et al. Quality of life in survivors of oronharvingeal cancer: A systematic
53 54	427	10.	rouiou and mote analysis of 1266 nationts. Fur L Concert 2017, 79 , p. 01, 102
55	420	10	Letter C.C. et al. Neuel nomegrame for survival and programming UDV.
56	429	19.	Larsen, C.G., et al., wover nomograms for survival and progression in HPV+ and HPV-
57	430		oropnaryngeai cancer: a population-basea study of 1,542 consecutive patients. Uncotarget,
58 50	431		2016. 7 (44): p. 71761-71772.
60	432	20.	Mehanna, H., et al., Prevalence of human papillomavirus in oropharyngeal and

Page 21 of 26

BMJ Open

1 2			
2 3	122		non-pronharmageal head and neck cancer-systematic review and meta-analysis of trends by
4	435		time and region. Head Neck 2013 25(5): p. 747-55
5	434	21	Lundherg M et al. Increased incidence of oronhanungeal cancer and n16 expression. Acta
0 7	435	21.	Otologing 2011 121(0): p 1008 11
8	430	22	D'Souza G et al. Case-control study of human nanillomavirus and oronharynaeal cancer N
9	437	22.	Engl Med 2007 256 (19): p. 1944-56
10	430	22	Cillison M Let al Endemiology of Human Panillomavirus Positive Head and Neck Saugmous
12	439	25.	Cell Carcinoma, I Clin Oncol, 2015, 22 (29): p. 2225-42
13	440	24	Sudboff H H at all Evidence for a causal association for HDV in head and neck cancers. Eur
14 15	441	24.	Arch Otorbinolaryngol 2011 268(11): p. 15/1-7
16	442	25	Ndiave C et al HBV DNA E6/E7 mRNA and p16/NK4a detection in head and neck cancers: a
17	445	23.	sustamatic review and mata anglusic. The Lancet Opcology, 2014, 15 (12): p. 1210, 1221
18 10	444	26	Corpon T et al. Breconting symptoms and clinical findings in HDV positive and HDV pagative
20	445	20.	carpen, 1., et al., Presenting symptoms and chinical jindings in Pro-positive and Pro-negative
21	440	77	Ang, K.K., et al. Human Banillamavirus and Survival of Patients with Oronhamagaal Cancer
22	447 110	27.	Ang, K.K., et al., Human Papinomaviras and Sarvival of Patients with Oropharyngeal Cancer.
23 24	440	20	New England Journal of Medicine, 2010. 303 (1). p. 24-55.
25	449	20.	(DRISMA D) 2015 statement Suct Day 2015 (11): p 1
26	450	20	(PRISIVIA-P) 2015 Statement. Syst Rev, 2015. 4(1), p. 1.
27 28	451	29.	the Cochrane collaboration 2 February 2022: Available from
20	452		the contraine conductation. 3 February 2023]; Available from:
30	455		<u>inteps://methods.cochrane.org/prognosis/sites/methods.cochrane.org.prognosis/mes/public</u>
31	454	20	<u>/uploads/protocol_template_prognosis_reviews.doc</u> .
32 33	455	30.	Collins, G.S., et al., Transparent reporting of a multivariable prediction model for individual
34	456		prognosis or alagnosis (TRIPOD): the TRIPOD statement. Journal of British Surgery, 2015.
35	457	24	102(3): p. 148-158.
36 37	458	31.	Moons, K.G.M., et al., PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction
38	459	- -	Model Studies: Explanation and Elaboration. Ann Intern Med, 2019. 170(1): p. w1-w33.
39	460	32.	Moons, K.G., et al., Critical appraisal and data extraction for systematic reviews of prediction
40	461		modelling studies: the CHARMS checklist. PLoS Med, 2014. 11 (10): p. e1001/44.
41 42	462	33.	Debray, T.P., et al., A guide to systematic review and meta-analysis of prediction model
43	463		performance. BMJ, 2017. 356 : p. 16460.
44	464	34.	Perry, A., et al., Therapeutic exercises for affecting post - treatment swallowing in people
45 46	465		treated for advanced - stage head and neck cancers. Cochrane Database of Systematic
47	466		Reviews, 2016(8).
48	467	35.	Chan, K.K.W., et al., Interventions for the treatment of oral and oropharyngeal cancers:
49 50	468		targeted therapy and immunotherapy. Cochrane Database of Systematic Reviews, 2015(12).
50 51	469	36.	McAleenan, A., et al., Prognostic value of test(s) for O6 - methylguanine – DNA
52	470		methyltransferase (MGMT) promoter methylation for predicting overall survival in people with
53	471		glioblastoma treated with temozolomide. Cochrane Database of Systematic Reviews, 2021(3).
54 55	472	37.	Kreuzberger, N., et al., Prognostic models for newly - diagnosed chronic lymphocytic
56	473		leukaemia in adults: a systematic review and meta - analysis. Cochrane Database of
57	474		Systematic Reviews, 2020(7).
58	475	38.	Aldin, A., et al., Interim PET - results for prognosis in adults with Hodgkin lymphoma: a
59 60	476		systematic review and meta - analysis of prognostic factor studies. Cochrane Database of

2			
3	477		Systematic Reviews, 2020(1).
4	478	39.	The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 3
5	479		February 2023]: Available from: https://training.cochrane.org/bandbook/current
7	480	40	Georging G L et al. Search filters for finding prognostic and diagnostic prediction studies in
8	400	40.	Madling to enhance systematic reviews Die Conc. 2012 7 (2): n. 222044
9	401		Wednine to enhance systematic reviews. PLos Offe, 2012. 7(2): p. e32844.
10	482	41.	Bramer, W.M., et al., De-duplication of database search results for systematic reviews in
11	483		<i>EndNote.</i> J Med Libr Assoc, 2016. 104 (3): p. 240-3.
12	484	42.	Stroup, D.F., et al., Meta-analysis of observational studies in epidemiology: a proposal for
14	485		reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA,
15	486		2000. 283 (15): p. 2008-12.
16	487	43.	Higgins, J.P., et al., Measuring inconsistency in meta-analyses, BMJ, 2003, 327 (7414); p. 557-
17	488		60
18 10	180	11	lorio A et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in
20	405		actimates of event rates in broad categories of patients, hmi, 2015, 250
21	490		estimates of event rates in broad categories of patients. binj, 2015. 550 .
22	491	45.	GRADE Handbook. Handbook for grading the quality of evidence and the strength of
23	492		recommendations using the GRADE approach: the GRADE working group. 3 February 2023];
24	493		Available from: https://gdt.gradepro.org/app/handbook/handbook.html .
23 26	494	46.	Hemingway, H., et al., Prognosis research strategy (PROGRESS) 1: a framework for researching
27	495		<i>clinical outcomes.</i> BMJ, 2013. 346 : p. e5595.
28	496	47.	Debray, T.P., et al., Meta-analysis and aggregation of multiple published prediction models.
29	497		Stat Med, 2014. 33 (14): p. 2341-62.
30 21			
32	498		
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Supplementary Table 1 The draft search strategy for MEDLINE

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Outcome = survival	Outcome = survival				
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References

- Ingui, B.J. and M.A. Rogers, *Searching for clinical prediction rules in MEDLINE*. J Am Med Inform Assoc, 2001. 8(4): p. 391-7.
- Geersing, G.J., et al., Search filters for finding prognostic and diagnostic prediction studies in Medline to enhance systematic reviews. PLoS One, 2012. 7(2): p. e32844.

Framing of this systematic review with key items identified by the CHARMS checklist^[1], which is the checklist for critical Appraisal and data extraction for systematic reviews of prediction modelling studies

Items	Comments	
1. Prognostic versus diagnostic	Prognostic prediction model (Aimed to predict future survival outcomes	
prediction model	of people diagnosed with OPSCC)	
2. Intended scope of the review	Prognostic prediction models to inform clinicians' therapeutic decision	
	making regarding the management of OPSCC	
3. Type of prediction modelling	All study types including prognostic prediction modelling studies (with	
studies	or without external validation) and external model validation studies	
	(with or without model updating)	
4. Target population to whom the	Patients diagnosed with OPSCC according to criteria in each eligible	
prediction model applies	study included in the review	
5. Outcome to be predicted	Future survival outcomes after diagnosis of OPSCC, including overall	
	survival (and/or disease-related mortality), progression-free survival, and	
	disease-free survival	
6. Time span of prediction	Survival outcomes occurring at any time point after diagnosis of OPSCC	
7. Intended moment of using the	At any time point after diagnosis of OPSCC	
model		

Notes: OPSCC, oropharyngeal squamous cell carcinoma.

References

1. Moons, K.G., et al., Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med, 2014. 11(10): p. e1001744.

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Prognostic prediction models for oropharyngeal squamous cell carcinoma (OPSCC): a protocol for systematic review, critical appraisal and meta-analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-073375.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Jul-2023
Complete List of Authors:	Lu, Zhen; Sun Yat-Sen University, School of Public Health (Shenzhen) Zhou, Xinyi; Sun Yat-Sen University, School of Public Health (Shenzhen) Fu, Leiwen; Sun Yat-Sen University, School of Public Health (Shenzhen) Li, Yuwei; Sun Yat-Sen University, School of Public Health (Shenzhen) Tian, Tian; Sun Yat-Sen University, School of Public Health (Shenzhen) Liu, Qi; Sun Yat-Sen University, School of Public Health (Shenzhen) Zou, Huachun; Fudan University, School of Public Health; Southwest Medical University, School of Public Health
Primary Subject Heading :	Oncology
Secondary Subject Heading:	Oncology, Public health, Qualitative research, Epidemiology
Keywords:	Systematic Review, ONCOLOGY, Prognosis, Head & neck tumours < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT
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4 5	1	Prognostic prediction models for oropharyngeal squamous cell carcinoma
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11 12 13	4	Zhen Lu ¹ , Xinyi Zhou ¹ , Leiwen Fu ¹ , Yuwei Li ¹ , Tian Tian ¹ , Qi Liu ¹ , Huachun Zou ^{2,3,4,*}
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16 17 18	6	¹ School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen 518107, China
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14 Abstract

Introduction: Oropharyngeal squamous cell carcinoma (OPSCC) is increasingly prevalent and has significantly heterogeneous risks of survival for diagnosed individuals due to the inter-related risk factors. Precise prediction of the risk of survival for an individual patient with OPSCC presents a useful adjunct to therapeutic decision making regarding the management of OPSCC. The aim of this systematic review, critical appraisal and meta-analysis is to assess prognostic prediction models for OPSCC and lay a foundation for future research programs to develop and validate prognostic prediction models for OPSCC.

Methods and analysis: This protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement. Based on predefined criteria, electronic databases including MEDLINE, Embase, Web of Science, the Cochrane Library and China National Knowledge Infrastructure (CNKI) will be searched for relevant studies without language restrictions from inception of databases to present. This study will systematically review published prognostic prediction models for survival outcomes in patients with OPSCC, describe their characteristics, compare performance, and assess risk of bias and real-world clinical utility. Selection of eligible studies, data extraction, and critical appraisal will be conducted independently by two reviewers. A Third reviewer will resolve any disagreements. Included studies will be systematically summarized using appropriate tools designed for prognostic prediction modelling studies. Risk of bias and quality of studies will be assessed using the Prediction Model Risk of Bias Assessment Tool and the Transparent

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Strengths and limitations of this study
This study will provide the comprehensive evidence on existing prognostic
prediction models for survival outcomes in patients with OPSCC.
The results will help us to analyze and assess the quality, risk of bias and clinical
utility of existing prognostic prediction models for survival outcomes in patients
with OPSCC.
The results of this review will provide insight that will assist in developing and

A highly sensitive search strategy and robust quality assessment criteria
(Transparent Reporting of a multivariable prediction model for Individual
Prognosis or Diagnosis) will be used to appraise existing prognostic prediction
modelling studies for OPSCC.

validating prognostic prediction models for OPSCC in future studies.

- 60 The main limitation of this study could be the potential heterogeneity among studies
- 61 included in the analysis.

64 Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is one of the head and neck carcinomas, which originates in tissues of the oropharynx (the part of the throat at the back of the mouth, including the soft palate, the base of the tongue, and the tonsils) [1-3]. OPSCC represents an increasingly prominent public health concern internationally. Albeit OPSCC only represents 0.9% of all cancers, its incidence has been rapidly growing worldwide in recent years, with an estimated 182666 new cases in 2020 [4-6]. An increased incidence of OPSCC among men under 45 years of age has been reported recently [6-9]. Moreover, the death rate of OPSCC is rising by 2% worldwide per year, compared with other head and neck carcinomas [10], with an estimated 86742 new deaths in 2020 [4]. Of note, OPSCC has a special feature of epidemiologic trends in different settings worldwide. Over the past few decades, OPSCC diagnosis increased especially in developed countries, including the United States, and Canada [6 11-13], while South-central Asia had the highest proportion of new OPSCC cases (35.1% of global incident cases) [14]. Across China, there has also been an obvious increase in OPSCC in the recent decade, especially for incidence and mortality of males and in rural areas, whereas the rates of females remained stable [15]. Compared with other common type of head and neck carcinomas, OPSCC is likely to be advanced (i.e., with neck metastases) at the time point of diagnosis and its primary treatment is more likely to be aggressive (such as radiation therapy and/or chemoradiation), which may have devastating effects on the survival of these patients [16-19]. OPSCC is a heterogeneous condition with inter-related factors significantly

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86 modifying the absolute risk of survival at an individual level.

Human papillomavirus (HPV) is considered to be the most significant risk factor for OPSCC [20-22]. HPV is a major carcinogen, which meets the epidemiological criteria for OPSCC causality [23 24]. Up to 70 % of newly diagnosed OPSCCs are HPV positive [25]. In addition, the current identified risk factors include heavy smoking and alcohol consumption [26]. However, it is worth noting that HPV-positive OPSCC patients are usually confronted with decades of significantly improved quality of life, compared to the HPV-negative OPSCC group of patients [19]. HPV-positive OPSCC is associated with a 58% reduction in the risk of death compared to its counterpart [27]. In contemporary real-world clinical practice, interventions (treatment and/or management) are implemented after diagnosis of OPSCC, without individualized risk assessment of the absolute risk of survival. Consequently, in case of immediate start of treatment after diagnosis of OPSCC, this mode of intervention fails to identify of the proportion of patients at high risk (with a lower probability to obtain a good response) who should have received new or more aggressive therapy regimens. Meanwhile, patients at low risk will not be spared from harm of unnecessary aggressive cancer treatment and significant financial burden of cancer management. Therefore, limitations of the one-size-fits-all mode of intervention and lack of risk-differentiated decision making are evident. In this regard, it is imperative to develop a precise and applicable prognostic prediction model for calculating the absolute risk of survival for patients with OPSCC, based on considering any relevant risk factors related to survival and individual demographical characteristics. Accurate prediction of risk of survival

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would then guide risk-differentiated clinical decision making at health services level,
ultimately, facilitate more personalized management of OPSCC and positively enhance
the quality of life of patients.

This systematic review will identify, screen, and assess all published prognostic prediction modelling studies for survival outcomes in patients with OPSCC. We aim to answer the question: what prognostic prediction models have been developed and validated for application in patients with OPSCC to predict risk of survival and inform clinicians' therapeutic decision making regarding the management of OPSCC. The detailed objectives of this systematic review are: 1. To systematically identify existing prognostic prediction models for survival outcomes in patients with OPSCC; 2. To qualitatively describe characteristics of identified models; 3. To quantitatively compare their performance across different clinical settings and population from different regions in the world with meta-analysis where appropriate; 4. To rigorously assess the conduct and real-world clinical utility of these prognostic prediction modelling studies.

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123 Methods

This systematic review protocol was registered on the PROSPERO international registry of systematic reviews on February 27, 2023 (CRD42023400272). This protocol for the systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline [28], Cochrane Prognosis Methods Group Protocol Template [29], transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)

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statement [30], PROBAST tool (prediction model risk of bias assessment) [31], and the
corresponding CHARMS checklist (checklist for critical Appraisal and data extraction
for systematic reviews of prediction modelling studies) [32] (see Supplementary Table
S1 and S2).

A systematic review of prognostic prediction modelling studies for survival outcomes in patients with OPSCC will be conducted to identify eligible studies published before March 2023. The review will be guided by the recommendations of The PROGnosis RESearch Strategy (PROGRESS) Partnership, which is an international, interdisciplinary collaboration that has published a framework to improve the standards of prognosis research to improve its translational impact. The framing of the review question is presented in Table 1. 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.

Table 1 Framing of this systematic review with key items identified by the CHARMS checklist [32]

Items	Comments		
1. Prognostic versus diagnostic	Prognostic prediction model (Aimed to predict future survival outcomes		
prediction model	of people diagnosed with OPSCC)		
2. Intended scope of the review	Prognostic prediction models to inform clinicians' therapeutic decision making regarding the management of OPSCC		
3. Type of prediction modelling	All study types including prognostic prediction modelling studies (with		
studies	or without external validation) and external model validation studies		
	(with or without model updating)		
4. Target population to whom the	Patients diagnosed with OPSCC according to criteria in each eligible		
prediction model applies	study included in the review		
5. Outcome to be predicted	Future survival outcomes after diagnosis of OPSCC, including overall		
	survival (and/or disease-related mortality), progression-free survival, and		
	disease-free survival		
6. Time span of prediction	Survival outcomes occurring at any time point after diagnosis of OPSCC		
7. Intended moment of using the	At any time point after diagnosis of OPSCC		
model			
Notes: OPSCC, oropharyngeal squamo	us cell carcinoma.		

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53	167	Table 2 Eligibility criteria for the sy	stematic review framed with the PICOTS syste	em [33]
54	168			
55	200	Items Inclusion	ocriteria	Exclusion criteria
56		Population Patients	diagnosed with OPSCC according to criteria	
57		in each e	ligible study included in the review	
58		Index Develop	ment or external validation of a prognostic	Diagnostic prediction models
59		predictio	n model for survival outcomes in patients	(e.g., diagnostic prediction
60		with OP	SCC (e.g., prognostic prediction models for	models for diagnosis of
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eligibility criteria f	framed with the PICOTS system, which it	is a modification of the		
established PICO system and designed for the specific requirements of systematic				
reviews of predicti	ion models with additional consideration	for timing and clinical		
setting [31].				
Table 2 Eligibility criteria	for the systematic review framed with the PICOTS syste	rm [33]		
Items	Inclusion criteria	Exclusion criteria		
Population	Patients diagnosed with OPSCC according to criteria in each eligible study included in the review			
Index	Development or external validation of a prognostic prediction model for survival outcomes in patients with OPSCC (e.g., prognostic prediction models for	Diagnostic prediction models (e.g., diagnostic prediction models for diagnosis of		
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	patients with OPSCC to predict survival outcomes)	OPSCC)
Comparator	No predefined comparator	
Outcomes (primary)	Overall survival (and/or disease-related mortality, if possible)	
Outcomes (secondary)	Progression-free survival, and disease-free survival	
Timing	Survival outcomes occurring at any time point after diagnosis of OPSCC	
Setting	Prognostic prediction models that are designed to be used by healthcare professionals in the clinical setting to inform their therapeutic decision making regarding the management of OPSCC, at any time point after diagnosis of OPSCC	
Study type	Any study design including primary research (e.g., randomized controlled trial, cohort study, case-control study) or secondary research (e.g., systematic review) that reports on one or more statistical models, tools or scores with at least two predictors proposed to predict an individual's risk of a future survival outcome (prognostic prediction modelling studies). Prognostic prediction modelling studies can be either model development, model validation or a combination	Editorial comments or letters

169 Notes: OPSCC, oropharyngeal squamous cell carcinoma.

171 **Population**

Studies reporting on prognostic prediction models proposed for survival outcomes in patients with OPSCC will be included into the systematic review. OPSCC could have been diagnosed according to criteria in each eligible study included in the review. In addition, this study will include both HPV-positive and HPV-negative OPSCC.

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177 Intervention

Prognostic prediction modelling studies (with or without external validation) and external model validation studies (with or without model updating) will be considered for inclusion into the systematic review, if they were intended to inform clinicians'

181 therapeutic decision making regarding the management of OPSCC.

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183 Outcome

184 The included outcome endpoints related to OPSCC, defined as the outcomes of interest

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in the eligibility criteria, are aligned with those agreed by consensus of systematic
reviews for treatment of OPSCC and draw on published search strategies for similar
review questions for prognostic models of cancers [16 17 27 34-38].

The primary outcome endpoint is overall survival (OS). We choose this endpoint because it has the greatest clinical relevance and is most important for patients diagnosed with OPSCC. Furthermore, OS is an objective endpoint not susceptible to bias of the outcome assessor. In addition, disease-related mortality will be considered if possible. The secondary outcome endpoints include progression-free survival (PFS) and disease-free survival (DFS). We choose these endpoints as patients with similar survival may nevertheless have different lengths of time without disease progression or symptoms, depending on both initial treatment after diagnosis and disease characteristics.

Outcome endpoints will be assessed in hierarchical fashion in the following order: OS (and/or disease-related mortality), PFS, and DFS. The timing and effect measures for each outcome endpoint will be as defined according to each eligible study included in the review. In addition, we will not require studies to have a minimum follow-up duration for inclusion in this systematic review. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

203 Timing

Each eligible study included in the review should report on prognostic prediction models for survival outcomes occurring at any time point after diagnosis of OPSCC.

Setting Prognostic prediction models that are designed to be used by healthcare professionals in the clinical setting, at any time point after diagnosis of OPSCC, will be considered for inclusion in the review. Type of studies and limits Any study design including primary research (e.g., randomized controlled trial, cohort study, case-control study) or secondary research (e.g., systematic review) that reports on one or more statistical models, tools or scores with at least two predictors proposed to predict an individual's risk of a future survival outcome (prognostic prediction modelling studies) will be considered for inclusion in the review. Prognostic prediction modelling studies can be either model development, model validation or a combination. Specifically, editorial comments or letters will be excluded from the review. Eligible studies included in the review will be limited to those conducted in humans by applying The Cochrane Group's filter for Humans not Animals filter [39]. Search methods for identification of studies **Databases** The following electronic databases will be systematically searched to identify eligible studies from their inception to present: 1) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily on Ovid and Ovid MEDLINE(R); 2) Embase Classic+Embase on Ovid; 3) Web of Science; 4) the

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229 Cochrane Library; and 5) China National Knowledge Infrastructure (CNKI).230

231 Search strategy

A highly sensitive search strategy, based on the eligibility criteria for the systematic
review and combining subject indexing terms (i.e., MeSH) and free-text search terms,
will be designed for MEDLINE Ovid. We aimed to avoid missing any valuable relevant
predictive modelling studies for OPSCC. The search strategy, specifically, subject
indexing terms will be translated appropriately for the other databases.

The draft search strategy will combine concepts related to prognostic prediction modelling studies, OPSCC, and survival outcomes. The updated version of a validated filter for prediction modelling studies [40] will be used. For OPSCC and survival outcomes related to OPSCC, a search strategy aligned with those agreed by consensus of peer-reviewed systematic reviews of treatments for OPSCC and drew on published search strategies for similar review questions for prognostic models of cancers will be used [16 17 27 34-38]. The draft search strategy is provided in Supplementary Table S3. The final search strategy will be iteratively refined.

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The reference lists of included model development studies and relevant systematic reviews for further studies will be hand searched for additional potentially relevant citations. The included studies will be checked for error or fraud. We will not place any restrictions on language, publication year or publication status when searching the electronic databases. Any non-English studies identified will be translated and assessed for eligibility.

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252	Data collection and analysis
253	Selection process
254	Two independent reviewers will screen and assess the abstracts of each study identified
255	by the final search strategy. Duplicate records will be excluded using a systematic,
256	rigorous and reproducible method utilizing a sequential combination of fields including
257	author, year, title, journal and pages [41]. Thereafter, if the information suggests that
258	the study meets the eligibility criteria for the review (Table 2) or there is any doubt
259	against eligibility, full texts of the studies will be independently accessed for further
260	assessment. Any conflict will be resolved through discussion with a senior advisor (HZ),
261	where required.
262	
263	Data extraction
264	Two independent reviewers will extract data from eligible studies included in the
265	review, using a standardized electronic form developed with reference to the checklist
266	for critical Appraisal and data extraction for systematic Reviews of prediction
267	Modelling Studies (CHARMS) [32].
268	For each eligible study, we plan to seek information on objective, source of data,
269	participants, survival outcome(s) to be predicted, candidate predictors, sample size,
270	missing data, model development, model performance (discrimination, calibration,
271	clinical utility, and measures of case-mix variation), results including final

multivariable models and interpretation of presented models, and model validation [32].

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Moreover, information on diagnostic criteria for OPSCC and treatment type after diagnosis will also be extracted. Missing data will be obtained from the study authors wherever possible, in addition, if insufficient information is obtained the study will be excluded from the review. Any disagreement will be resolved through consultation with a senior advisor (HZ), when necessary.

Data management

Covidence systematic review software will be used to manage screened records
throughout the review (Veritas Health Innovation, Melbourne, Australia. Available at:
<u>http://www.covidence.org</u>). Eligible studies included in the review will be imported
into Endnote reference manager software (Version 20.4.1, Clarivate Analytics,
Philadelphia, USA. Available at: <u>https://endnote.com/</u>).

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286 Critical appraisal

The methodological quality (risk of bias) and relevance (applicability) to the review question (Table 1 and 2) of eligible studies included in the review will be systematically assessed using the prediction model risk of bias assessment tool (PROBAST) [31]. This tool is structured around four key domains (participants, predictors, outcome, and analysis), of which each will be rated as high, low, or unclear risk of bias.

Two independent reviewers will assess the risk of bias and applicability of each eligiblestudy included in the review. Each study will be given a rating of high, low, or unclear

risk for each of the four domains. Any disagreement will be resolved through discussion

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and consultation with a senior advisor (HZ) to reach a consensus, where required.

Qualitative data synthesis of prognostic prediction models

All extracted data on prognostic prediction models from included studies will be tabulated to facilitate comparison of survival outcomes to be predicted, predictors included in the final model and performance measures [32]. Measures of uncertainty will be reported when published or approximated using published methods [33]. The characteristics of models will be tabulated to show classification measures such as sensitivity, specificity, area under the receiver operating characteristic curve (AUROC) [32], 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-4.0 project.org).

Quantitative analysis and comparison of the predictive performance of prognostic prediction models

Our quantitative analysis will depend on the data available, the final number of eligible prognostic prediction models included in the review, and the type of prognostic prediction modelling studies (i.e., development or validation).

We will attempt a meta-analysis by type of prognostic prediction modelling studies, if included studies are sufficiently homogenous. Clinical homogeneity will be regarded as satisfied, if the review identifies: 1) multiple validation studies for a common prognostic prediction model are identified or, 2) multiple development studies where

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the target population to whom the model applies, and survival outcomes to be predictedare considered similar or the same.

320 Meta-analysis and investigation of heterogeneity

Where data permits, meta-analysis will be conducted with reference to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group guidelines [42]. 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 [39], which provide estimates of the average performance of predictive models across the selected modelling studies. The restricted maximum likelihood and Hartung-Knapp-Sidik-Jonkman methods will be used to estimate the between-study heterogeneity and 95% confidence intervals for the average performance [33].

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Statistical or clinical homogeneity will be assessed using the I^2 test, where an I^2 value > 50% indicates moderate to high heterogeneity, as specified in published literatures [39 43]. 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:

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https://www.R-project.org).

Subgroup analysis

Where there are enough eligible studies included in the review, we planned to conduct subgroup analyses. Subgroup analyses will be undertaken according to the type of prognostic prediction modelling studies (i.e., development or validation), target population to whom the model applies, diagnostic criteria for OPSCC, whether population was treated (yes/no), treatment type after diagnosis, the follow-up duration, survival outcomes to be predicted, and study quality (risk of bias).

349 Sensitivity analysis

If meta-analysis would be performed, we would undertake sensitivity analyses to explore the influence on effect size for exclusion of studies at lower and higher risk of bias³³.

354 Summary of findings

Reporting and presentation of findings will be guided by the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses) [28], and relevant recommendations from the TRIPOD statement (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) [30]. The GRADE approach (grading of recommendations, assessment, development and evaluation) will be utilized to determine confidence in estimates [44 45].

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362 **Discussion**

This systematic review will identify, screen, and assess all published prognostic prediction models for survival outcomes in patients with OPSCC. All eligible models included in the review will be systematically summarized and compared for their performance across different clinical settings and population from different regions in the world with meta-analysis if feasible.

A prognostic prediction model for survival outcomes in patients with OPSCC is 368 369 designed to be used by healthcare professionals in the clinical setting to inform their therapeutic decision making regarding the management of OPSCC, at any time point 370 after diagnosis of OPSCC. Compared with other common types of head and neck 371 372 carcinomas, OPSCC is likely to be advanced (i.e., with neck metastases) at the time point of diagnosis and its primary treatment is more likely to be aggressive (such as 373 radiation therapy and/or chemoradiation), which may have devastating effects on the 374 survival of these patients [16-19]. Survival outcomes affecting the quality of life of 375 these patients are of utmost importance. Hence, accurate prediction of risk of survival 376 would guide risk-differentiated clinical decision making at health services level, 377 ultimately, facilitate more personalized management of OPSCC and positively enhance 378 the quality of life of patients. Consequently, in case of immediate start of treatment after 379 diagnosis of OPSCC, identification of patients with a lower probability to obtain a good 380 381 response will aid in making decisions regarding management, for instance, deciding new or more aggressive therapy regimens would be delivered to this proportion of 382

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patients at high risk. In contrast, in case of a watch-and-wait strategy, differences in
estimated prognostic survival risks can affect patient management regarding
surveillance and treatment.

Prognosis-related research in OPSCC has been seeking to predict risk of survival after diagnosis based on routinely collected data, with a view to directing treatment and/or management efforts in real-world clinical practice. This systematic review will make an important contribution to the understanding of risk of survival for patients diagnosed with OPSCC. Moreover, each eligible prognostic prediction models included will be compared head-to-head for their performance and clinical utility in the review. From this perspective, the review will comprehensively promote the consideration of risk-differentiated clinical management of OPSCC in real-world practice. Furthermore, in case that insufficient applicable models are identified, or screened models have poor performance, and/or high risk of bias, we will provide explicit rationale and detailed guidance for development, validation, and/or updating for prognostic prediction models for OPSCC. In contrast, in case that high-performance models are identified, they will be valuable to helping clinicians and patients with OPSCC understand and consider estimated risk of survival in shared decision making, objectively and systematically.

As such, this systematic review forms the foundations of future research programs to
develop, validate, and assess a prognostic prediction model for OPSCC across the four
themes of the PROGRESS prognosis research framework [46]. We noted that
researchers have been focusing efforts on developing new prognostic prediction models
to date, however, disproportionate efforts have been put into improving and ultimately

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405 implementing existing models into real-world clinical practice, which have caused a
406 huge waste of research resources. Therefore, we strongly recommend that, in the future,
407 researchers could optimally utilize information from our review. If appropriate, seeking
408 to validate and update existing prognostic prediction models would be better choice
409 [47].

In conclusion, this systematic review will comprehensively consider contemporary best
practice and evidence of prognostic prediction modelling studies for OPSCC. This work
will support risk-differentiated clinical decision making at health services level,
ultimately, facilitate more personalized management of OPSCC and positively enhance
the quality of life of patients.

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funding parties did not have any role in the design of the study or in the explanation of
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Contributors

ZL and HZ conceived the study and designed the protocol. ZL, XZ, LF, YL, TT, and
QL contributed to the manuscript with all authors critically revising the manuscript. All
authors have read and approved the final version of the manuscript.

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428	This study was supported by the Natural Science Foundation of China Excellent Young
429	Scientists Fund [82022064] and Merck Investigator Studies Program [100073].
430	
431	Competing interest
432	None declared.
433	
434	Data availability statement
435	No data are available. The study is a protocol for a systematic review. Thus, no data are
436	available.
437	
438	ORCID ID
439	Zhen Lu, <u>https://orcid.org/0000-0002-3481-6310</u>
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2		
3	440	Deferences
4 5	442	Kelerences
6	443	1. Shibahara T. [Oral cancer -diagnosis and therapy]. Clin Calcium 2017;27(10):1427-33.
7	444	2. Gooi Z, Chan JY, Fakhry C. The epidemiology of the human papillomavirus related to oropharyngeal
8	445	head and neck cancer. Laryngoscope 2016;126(4):894-900. doi: 10.1002/lary.25767
9 10	446	[published Online First: 20160204]
11	447	3. Definition of Oropharyngeal Cancer—NCI Dictionary of Cancer Terms—National Cancer Institute [5
12	448	December 2022]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-
13 14	449	terms/def/oropharyngeal-cancer.
15	450	4. Sung H. Ferlay I. Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and
16	451	Mortality Worldwide for 36 Cancers in 185 Countries. <i>CA Cancer J Clin</i> 2021;71(3):209-49. doi:
17	452	10 3322/caac 21660 [nublished Online First: 20210204]
18	453	5 De Felice E Tombolini V Valentini V et al Advances in the Management of HPV-Related
20	455	Oronbaryngeal Cancer / Oncol 2010-2010-0172720 doi: 10.1155/2010/0173720 [published
21	455	Online Eirct: 201004141
22	455	Chaturuedi AK, Anderson WE, Lortet Tieulent L et al. Worldwide trends in incidence rates for eral
23 24	450	o. Charactive and propher model concerts / <i>Clin</i> Once/ 2012;21/26):4EEO 0 doi:
25	457	Cavity and oropharyngeal cancers. J Clin Oncol 2013;31(36):4550-9. doi:
26	458	
27	459	7. Abram MH, van Heerden WF, Rheeder P, et al. Epidemiology of oral squamous cell carcinoma. SADJ
28 29	460	2012;67(10):550-3.
30	461	8. Majchrzak E, Szybiak B, Wegner A, et al. Oral cavity and oropharyngeal squamous cell carcinoma in
31	462	young adults: a review of the literature. <i>Radiol Oncol</i> 2014;48(1):1-10. doi: 10.2478/raon-
32	463	2013-0057 [published Online First: 20140122]
33 34	464	9. Auluck A, Walker BB, Hislop G, et al. Population-based incidence trends of oropharyngeal and oral
35	465	cavity cancers by sex among the poorest and underprivileged populations. BMC Cancer
36	466	2014;14(1):316. doi: 10.1186/1471-2407-14-316
37	467	10. Lee SC, Leung KKC, Chung ACY, et al. Fluid Biomarkers in HPV and Non-HPV Related Oropharyngeal
38 39	468	Carcinomas: From Diagnosis and Monitoring to Prognostication-A Systematic Review. Int J Mol
40	469	<i>Sci</i> 2022;23(22) doi: 10.3390/ijms232214336 [published Online First: 20221118]
41	470	11. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates:
42	471	differences by country, sex and anatomic site. Oral Oncol 2014;50(5):387-403. doi:
45 44	472	10.1016/j.oraloncology.2014.01.016 [published Online First: 20140213]
45	473	12. Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinomaan update. CA
46	474	Cancer J Clin 2015;65(5):401-21. doi: 10.3322/caac.21293 [published Online First: 20150727]
47 49	475	13. Lambert R, Sauvaget C, de Camargo Cancela M, et al. Epidemiology of cancer from the oral cavity
40 49	476	and oropharynx. Eur J Gastroenterol Hepatol 2011;23(8):633-41. doi:
50	477	10.1097/MEG.0b013e3283484795
51	478	14. Shield KD, Ferlay J, Jemal A, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by
52 53	479	subsite in 2012. CA Cancer J Clin 2017;67(1):51-64. doi: 10.3322/caac.21384 [published Online
55	480	First: 20161019]
55	481	15. Liu J. Yang XI. Zhang SW. et al. Incidence mortality and temporal patterns of propharyngeal cancer
56	482	in China: a population-based study <i>Cancer Commun (Lond)</i> 2018-38(1):75 doi:
57 58	483	10 1186/s40880-018-0345-5 [nubliched Online First: 20181229]
59	484	16 Parmar A Macluskey M Mc Goldrick N et al Interventions for the treatment of oral cavity and
60	704	To rama A, machaskey w, we downed w, et al. merventions for the treatment of oral davity and
		22

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2		
3	485	oropharyngeal cancer: chemotherapy. Cochrane Database of Systematic Reviews 2021(12) doi:
4 5	486	10.1002/14651858.CD006386.pub4
6	487	17. Howard J, Dwivedi RC, Masterson L, et al. De - intensified adjuvant (chemo)radiotherapy versus
7	488	standard adjuvant chemoradiotherapy post transoral minimally invasive surgery for resectable
8 9	489	HPV - positive oropharyngeal carcinoma. Cochrane Database of Systematic Reviews 2018(12)
10	490	doi: 10.1002/14651858.CD012939.pub2
11	491	18. Hoxbroe Michaelsen S, Gronhoj C, Hoxbroe Michaelsen J, et al. Quality of life in survivors of
12	492	oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. Eur J Cancer
14	493	2017;78:91-102. doi: 10.1016/j.ejca.2017.03.006 [published Online First: 20170418]
15	494	19. Larsen CG, Jensen DH, Carlander AF, et al. Novel nomograms for survival and progression in HPV+
16	495	and HPV- oropharyngeal cancer: a population-based study of 1,542 consecutive patients.
17 18	496	Oncotarget 2016;7(44):71761-72. doi: 10.18632/oncotarget.12335
19	497	20. Mehanna H, Beech T, Nicholson T, et al. Prevalence of human papillomavirus in oropharyngeal and
20	498	nonoropharyngeal head and neck cancersystematic review and meta-analysis of trends by
21	499	time and region. Head Neck 2013;35(5):747-55. doi: 10.1002/hed.22015 [published Online
22	500	First: 20120120]
24	501	21. Lundberg M, Leivo I, Saarilahti K, et al. Increased incidence of oropharyngeal cancer and p16
25	502	expression. Acta Otolaryngol 2011;131(9):1008-11. doi: 10.3109/00016489.2011.575796
26 27	503	[published Online First: 20110504]
28	504	22. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and
29	505	oropharyngeal cancer. N Engl J Med 2007;356(19):1944-56. doi: 10.1056/NEJMoa065497
30 31	506	23. Gillison ML, Chaturvedi AK, Anderson WF, et al. Epidemiology of Human Papillomavirus-Positive
32	507	Head and Neck Squamous Cell Carcinoma. J Clin Oncol 2015;33(29):3235-42. doi:
33	508	10.1200/JCO.2015.61.6995 [published Online First: 20150908]
34	509	24. Sudhoff HH, Schwarze HP, Winder D, et al. Evidence for a causal association for HPV in head and
36	510	neck cancers. Eur Arch Otorhinolaryngol 2011;268(11):1541-7. doi: 10.1007/s00405-011-
37	511	1714-8 [published Online First: 20110727]
38	512	25. Ndiaye C, Mena M, Alemany L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and
39 40	513	neck cancers: a systematic review and meta-analysis. The Lancet Oncology 2014;15(12):1319-
41	514	31.
42	515	26. Carpen T, Sjoblom A, Lundberg M, et al. Presenting symptoms and clinical findings in HPV-positive
43 44	516	and HPV-negative oropharyngeal cancer patients. Acta Otolaryngol 2018;138(5):513-18. doi:
45	517	10.1080/00016489.2017.1405279 [published Online First: 20171121]
46	518	27. Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with
47	519	Oropharyngeal Cancer. New England Journal of Medicine 2010;363(1):24-35. doi:
40 49	520	10.1056/NEJMoa0912217
50	521	28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-
51	522	analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ : British Medical Journal
52 53	523	2015;349:g7647. doi: 10.1136/bmj.g7647
54	524	29. Cochrane Prognosis Methods Group. Cochrane prognosis methods group protocol template: the
55	525	Cochrane collaboration [Available from:
56 57	526	https://methods.cochrane.org/prognosis/sites/methods.cochrane.org.prognosis/files/public
58	527	/uploads/protocol_template_prognosis_reviews.doc accessed 3 February 2023.
59	528	30. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model
60		

2		
3	529	for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Journal of British
4	530	Surgery 2015;102(3):148-58.
6	531	31. Moons KGM, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of
7	532	Prediction Model Studies: Explanation and Elaboration. Ann Intern Med 2019:170(1):W1-W33.
8	533	doi: 10 7326/M18-1377
9 10	53/	32 Moons KG, de Groot IA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic
10	525	s2. Woons KG, de Groot SA, bodwhilesser W, et di. entied approval and data extraction of systematic
12	535	2014.11(10).01001744 doi: 10.1271/journal.nmod.1001744 [nublished Online First:
13	550	2014,11(10).e1001744. doi: 10.1371/journal.priled.1001744 [published Online First.
14 15	537	
15 16	538	33. Debray TP, Damen JA, Snell KI, et al. A guide to systematic review and meta-analysis of prediction
17	539	model performance. BMJ 2017;356:i6460. doi: 10.1136/bmj.i6460 [published Online First:
18	540	20170105]
19	541	34. Perry A, Lee SH, Cotton S, et al. Therapeutic exercises for affecting post - treatment swallowing in
20	542	people treated for advanced - stage head and neck cancers. Cochrane Database of Systematic
21	543	Reviews 2016(8) doi: 10.1002/14651858.CD011112.pub2
23	544	35. Chan KKW, Glenny AM, Weldon JC, et al. Interventions for the treatment of oral and oropharyngeal
24	545	cancers: targeted therapy and immunotherapy. Cochrane Database of Systematic Reviews
25 26	546	2015(12) doi: 10.1002/14651858.CD010341.pub2
20 27	547	36. McAleenan A, Kelly C, Spiga F, et al. Prognostic value of test(s) for O6 - methylguanine - DNA
28	548	methyltransferase (MGMT) promoter methylation for predicting overall survival in people
29	549	with glioblastoma treated with temozolomide. Cochrane Database of Systematic Reviews
30	550	2021(3) doi: 10 1002/14651858 CD013316 pub2
31 32	551	37 Kreuzberger N. Damen I. Trivella M. et al. Prognostic models for newly - diagnosed chronic
33	552	lymphocytic leukaemia in adults: a systematic review and meta - analysis. Cochrane Database
34	552	of Systematic Paviance 2020(7) doi: 10.1002/14651858 CD012022 pub2
35	555	0) Systematic Reviews 2020(7) doi: 10.1002/14051858.CD012022.pub2
36 37	554	38. Aldin A, Omiaun E, Estcourt E, et al. Interim PET - results for prognosis in addits with Hodgkin
38	555	lymphoma: a systematic review and meta - analysis of prognostic factor studies. <i>Cochrane</i>
39	556	Database of Systematic Reviews 2020(1) doi: 10.1002/14651858.CD012643.pub3
40	557	39. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions [Available
41 42	558	from: https://training.cochrane.org/handbook/current accessed 3 February 2023.
42 43	559	40. Geersing GJ, Bouwmeester W, Zuithoff P, et al. Search filters for finding prognostic and diagnostic
44	560	prediction studies in Medline to enhance systematic reviews. <i>PLoS One</i> 2012;7(2):e32844. doi:
45	561	10.1371/journal.pone.0032844 [published Online First: 20120229]
46 47	562	41. Bramer WM, Giustini D, de Jonge GB, et al. De-duplication of database search results for systematic
47 48	563	reviews in EndNote. J Med Libr Assoc 2016;104(3):240-3. doi: 10.3163/1536-5050.104.3.014
49	564	42. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a
50	565	proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE)
51	566	group. JAMA 2000;283(15):2008-12. doi: 10.1001/jama.283.15.2008
5∠ 53	567	43. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ
55	568	2003;327(7414):557-60. doi: 10.1136/bmi.327.7414.557
55	569	44. Jorio A. Spencer FA. Falavigna M. et al. Use of GRADE for assessment of evidence about prognosis
56	570	rating confidence in estimates of event rates in broad categories of natients <i>hmi</i> 2015-350
57 58	571	45 GRADE Handbook Handbook for grading the quality of evidence and the strength of
59	571	The strength of the contract the contract the contract the contract of the strength of the str
60	572	recommendations using the GRADE approach: the GRADE working group [AVailable from:

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4	573	https://gdt.gradepro.org/app/handbook/handbook.html accessed 3 February 2023.
5	574	46. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for
6	575	researching clinical outcomes. BMJ 2013;346:e5595. doi: 10.1136/bmj.e5595 [published
7	576	Online First: 20130205]
0 9	577	47. Debray TP, Koffijberg H, Nieboer D, et al. Meta-analysis and aggregation of multiple published
10	578	prediction models. Stat Med 2014;33(14):2341-62. doi: 10.1002/sim.6080 [published Online
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Section and topic	Item N		Page Number
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Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing add so discover author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such the changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:		AII	
Sources	5a	Indicate sources of financial or other support for the review	20
Sponsor	5b	Provide name for the review funder and/or sponsor	20
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	20
INTRODUCTION		sir on	
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interpentions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial register or other grey literature sources) with planned dates of coverage	6-11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11-12, Supplementary Table S3
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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each \vec{p}_{ase} as \vec{b}_{ase} the review (that is, screening, eligibility and inclusion in meta-analysis)	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in deplicate), any processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be at the outcome or study level, or both; state how this information will be used in data synthesis	-
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling $data$ and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	
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	11	exp Otorhinolaryngologic Neoplasms/
	12	exp Neoplasms/
	13	(cancer\$ or tumour\$ or tumor\$ or neoplas\$ or malignan\$ or
		carcinoma\$ or SCC\$).ti,ab.
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		neck" or "head-neck" or "head-and-neck" or tongue\$).ti,ab.
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Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
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Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such the changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	20
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INTRODUCTION		sir ê	
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interpentions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-1
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11-12 Suppleme Table
Study records:			
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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review C C C C C C C C C C	12-17
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each \vec{p}_{ase} f the review (that is, screening, eligibility and inclusion in meta-analysis)	12-17
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in deplicate), any processes for obtaining and confirming data from investigators	12-17
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-	6-17
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional	6-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be the outcome or study level, or both; state how this information will be used in data synthesis	6-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12-17
2	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling that and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	12-17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12-17
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12-17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6-17
* It is strongly recommende	d that th	is checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important chriftication on the items. Amendments to a	a review prot
* It is strongly recommende should be tracked and dated	d that th	is checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important control on the items. Amendments to pyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Common on June 11, 2025 and similar technologies.	a review prot
* It is strongly recommende should be tracked and dated	ed that th I. The co	is checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important of prification on the items. Amendments to pyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Common and Similar technologies. Similar technologies.	a review p

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Supplementary Table S2. The C	CHARMS checklist ²	
Items	Comments from Comments	
 Prognostic versus diagnostic prediction model Intended scope of the review 	Prognostic prediction model (Aimed to predict future survival outcomes of people diagnosed with OPSCC) Prognostic prediction models to inform clinicians' therapeutic decision	
3. Type of prediction modelling studies	making regarding the management of OPSCC All study types including prognostic prediction modelling studies (with or without external validation) and external model validation studies	
 Target population to whom the prediction model applies Outcome to be predicted 	(with or without model updating) Patients diagnosed with OPSCC according to criteria in each eligible study included in the review Future survival outcomes after diagnosis of OPSCC, including overall survival (and/or disease-related mortality), progression-free survival,	
6. Time span of prediction	and disease-free survival Survival outcomes occurring at any time point after diagnosis of OPSCC	
7. Intended moment of using the model	At any time point after diagnosis of OPSCC	
otes: OPSCC, oropharyngeal squamous o	cell carcinoma.	
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Reference

1. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* : *British Medical Journal* 2015;349:g7647. doi: 10.1136/bmj.g7647

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2. 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]