

Characteristics of Systematic Reviews on Oral Cancer Detection: A Protocol Analysis Based on PROSPERO

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Systematic Review

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Abstract

This study examined 101 registered protocols of systematic reviews on oral cancer detection from the PROSPERO registry. Most were registered in 2023 and originated from 84 institutions in 30 countries, with India contributing the most. Santiago de Compostela University had the highest institutional representation. Most protocols (90.3%) are still under review, with a few published. Financial support was absent in 72.2%. Risk of bias was commonly assessed using QUADAS-2. Data analysis methods varied, with many unspecified. RevMan was the preferred software. Observational studies dominated, and most protocols used PubMed and Scopus. Biomarkers were the most frequently studied intervention.

Introduction

A systematic review is a highly reliable and comprehensive research method that synthesises all existing evidence on a specific research topic using a structured and systematic approach (Schiavo, 2019). It is more rigorous than traditional narrative reviews because it involves a comprehensive literature search, critical evaluation, and synthesis of all reliable evidence on a specific subject (Fu et al., 2023). Systematic reviews offer comprehensive, high-quality summaries that help policy-making decisions and identify the current research landscape by systematically analyzing a wide range of evidence (Munn, Stern, Aromataris, Lockwood, & Jordan, 2018). Systematic reviews can be either quantitative (meta-analysis) or qualitative. Meta-analysis is a quantitative statistical method used to combine the results of original studies (Fernandes et al., 2018; Moher, Liberati, Tetzlaff, Altman, & PRISMA Group*, 2009).

Protocol registration is essential in conducting systematic reviews, as it provides a clear and transparent framework for the review process before data collection and analysis commence (Page, Shamseer, & Tricco, 2018; Schiavo, 2019). Registries such as PROSPERO enable researchers to showcase the key methodological details, supporting the rigor and accountability of their work (Alison Booth et al., 2012). In this study, we assess and analyse protocols of systematic reviews on oral cancer detection registered in PROSPERO, with the core objective of identifying the characteristics of these reviews and other bibliometric aspects such as institutional representation and geographical distribution.

PROSPERO is an international database for registering systematic review protocols, mainly in medicine and health care. Launched in 2011 and managed by the Centre for Reviews and Dissemination at the University of York. By allowing researchers to publish their methodological details and review plans detailed plans before starting data collection and analysis, PROSPERO aims to improve research transparency, reduce duplication, and minimize bias (Borah, Brown, Capers, & Kaiser, 2017; Sideri, Papageorgiou, & Eliades, 2018). It is financially Supported by the UK's National Institute for Health Research. It is free to access and use, making it a valuable resource for improving the quality and credibility of systematic reviews (Schiavo, 2019).

Oral cancer is a multifactorial disease that continues to be a significant health challenge. Genetic, epigenetic and environmental factors significantly increase the risk of oral cancer (Girardi, Schuch, &

Martins, 2024; Ramachandran, 2024). According to the WHO GLOBOCAN 2022 report, oral cancer is the 16th most common cancer globally. It accounted for 389846 cases worldwide with an age-standardised rate (ASR) of incidence of 4.0. In India, the ASR of incidence and mortality is 9.9 and 5.6, respectively (Wéber et al., 2024). Oral cancer can affect various anatomical sites, including the lip, tongue, floor of the mouth, cheek, gingiva, and hard and soft palate (Ramachandran, 2024). Oral cancer is generally preceded by the occurrence of pre-cancerous lesions called Oral Potentially Malignant Disorders (OPMD). Early identification of OPMDs can reduce the risk of the development of oral cancer. Currently available detection methods include visual oral examination, vital staining, oral cytology, optical imaging, biopsy, biomarkers and other molecular techniques (Su et al., 2021). Early detection and evaluation of both pre-cancerous lesions and oral cancer can drastically improve the prognosis, increase the overall survival rate, improve the quality of life of patients and reduce treatment-related morbidity (Jain, 2024).

Materials and Methods

2.1 Data Source

The protocols on the detection of oral cancer analysed were retrieved from the PROSPERO registration platform, accessible at <https://www.crd.york.ac.uk/prosperto/>. Data was collected on August 8, 2024. The default filters available on PROSPERO were used to refine the results.

2.2 Inclusion And Exclusion Criteria

The studies included in the protocols were those registered as systematic reviews on PROSPERO. The study population consisted of patients with oral cancer, and the interventions focused on detecting oral cancer using biomarkers, screening tests, or computer-based detection/diagnostic algorithms. Systematic reviews involving animals and duplicate documents were excluded from the analysis.

Study Selection and Duplicate Removal

Initially, a data set of 153 registered protocols was retrieved. The bibliographic details of these protocols were downloaded. The data set was refined again using inclusion-exclusion criteria and by removing duplicates, resulting in N = 101 registered protocols. The first author manually entered the data into Microsoft Excel. The second author reviewed, screened, and verified the accuracy of the data collected. Duplication removal was conducted in two phases: the first used EndNote reference management software, and the second was done manually, ultimately identifying 101 appropriate systematic reviews for the final study selection. Each data variable was colour-coded, and Microsoft Excel was utilised for data structuring and descriptive analysis.

Results

3.2 General Characteristics of Selected Systematic Reviews

Initially, 153 systematic review protocols were retrieved. After applying inclusion-exclusion criteria and removing duplicates, the query returned 101 highly relevant systematic review protocols on oral cancer detection. The early systematic review on the detection of oral cancer was registered in 2014. However, most registrations—28 out of 101 (27.2%)—occurred in 2023. There has been a significant increase in registrations since 2020, with 11 (10.7%) in 2020, 12 (11.7%) in 2021, 17 (16.5%) in 2022, 28 (27.2%) in 2023, and 17 (16.5%) in 2024 (Table 1). It's important to note that the 2024 data is incomplete, covering only January to July, so the number of registrations for that year will likely increase.

As of August 8, 2024, only 5 systematic reviews (2.9%) had reached their expected completion time and been published. Three additional systematic reviews have completed the review process but have not yet been published in a journal. Table 1 shows that the majority 90.3% (n = 93) of registered systematic reviews are still undergoing the review process.

Regarding the chosen language for registered systematic reviews, English is the predominant choice, with approximately 99% (n = 100) of the systematic reviews on the detection of oral cancer conducted in English. Two systematic reviews (2%) are in Spanish. Additionally, three systematic reviews are bilingual, incorporating Indonesian, Chinese, and Portuguese (Brazil) alongside English.

Concerning the number of reviewers, 3 systematic reviews have a single reviewer, 22 (21.8%) systematic reviews are conducted by two reviewers, and another 22 (21.8%) have three reviewers. Following this, 17 systematic reviews (16.8%) have four reviewers, 13 (12.9%) have five reviewers, 11 (10.9%) have six reviewers, and 10 (9.9%) have seven reviewers. One systematic review has nine, eleven, and twelve reviewers.

Research funding details from the registered protocols revealed that 73 systematic reviews (72.2%) are either self-funded by the reviewers or have no funding, while only 28 (27.7%) are funded. Of the funded reviews, 13 are supported by various universities and research institutes, including Semmelweis University, University of Foggia, Government Dental College and Hospital, Mumbai, National Cancer Institute (NCI), James Cook University, National Institutes of Health/NIDCR, Jiangsu Higher Education Institutions, University of Saskatchewan, University of Talca, University of Campania Luigi Vanvitelli, University of Florence, Laboratory of Pathology and Molecular Biology - Faculty of Dentistry, and Charité – Universitätsmedizin Berlin. Two reviews received direct ministerial-level funding from the Ministry of Health, Sultanate of Oman, and the Taiwan Ministry of Science and Technology.

Other funding sources include The Coordination of Improvement of Higher Education Personnel (CAPES), Brazil, which funded three reviews, and various organizations such as DBT/Wellcome Trust India Alliance, São Paulo Research Foundation (Brazil), Health Technology Assessment Project (India), Latin American Network of Pediatrics and Neonatology, Research Project of Higher Education Teaching

Reform in Hainan Province, the Open Project Program of Xinjiang Key Laboratory of Cloud Computing Applications (China), National Natural Science Foundation of China, and the Chinese Center for Disease Control and Prevention, each supporting one review. Additionally, one systematic review is financially supported by Prof. Pantelis V. Rados of Universidade Federal do Rio Grande do Sul, and another is funded through a postdoctoral fellowship; all details are displayed in Table 1.

3.3 Quality assessment of selected Systematic Reviews

All 101 selected systematic review protocols reported assessing the Risk of bias in the included studies. However, 8 did not specify the tool they used for this assessment. The most used tool was the “*Quality Assessment of Diagnostic Accuracy Studies 2*”(QUADAS-2 guideline), employed in 32 systematic reviews. The “*Newcastle-Ottawa Quality Assessment Scale (NOS)*” was the second most frequently used, appearing in 19 studies, followed by the “*Cochrane Collaboration's 'Risk of Bias' tool (RoB2)*”, used in 9 studies. The tools used and their respective counts are presented in Table 2.

3.4 Reported Data Synthesis Method and Tool Used for Data Analysis

Of the protocols, 34 selected quantitative synthesis as their data synthesis method, 21 chose narrative synthesis, and 10 used both narrative and quantitative methods. All 101 protocols reported their data analysis strategy; however, 67 did not specify the data analysis or statistical software they used. Review Manager (RevMan) was the most reported software, used by 19 protocols, followed by STATA, used by 11 protocols, and the R statistical package, used by 7 protocols. 5 protocols used SPSS, while MedCalc, Prometa, and MetaDisc were each used by one protocol. Additionally, some protocols utilised reference management software like EndNote and Mendeley for data extraction, screening, and duplicate removal. All details are presented in Table 3.

3.5 Type of included studies

The research studies included in the selected systematic review protocols are categorised into three groups: studies with no inclusion restrictions, observational, and experimental. Notably, 25 (12.8%) protocols did not restrict the type of studies included. Observational studies were the most common, with 122 studies (62.2%), while experimental studies comprised 25% (49). Table 4 presents detailed information on the types of observational and experimental studies and their respective counts.

3.6 Database

Among the selected systematic review protocols, only 41 (40.6%) provided a detailed search strategy, including information on selected or searched databases, inclusion and exclusion criteria, search terms (such as MeSH or free text terms), and structured search queries using Boolean or proximity operators. However, 60 (59.4%) protocols did not report a search strategy; some mentioned only the database names. All selected protocols reported the databases they searched, with PubMed/Medline being the most frequently used, appearing in 100 (99.0%) protocols. Other commonly used databases included Scopus (67, 66.3%), Web of Science (55, 54.5%), Embase (52, 51.5%), Cochrane Library (43, 42.6%), and

Google Scholar (35, 34.7%). The complete list of reported databases and their respective counts is provided in Table 5.

Regarding the combination of databases, 2 systematic review protocols do not integrate multiple databases; they depend on PubMed only. Five integrate two databases, 15 integrate three databases, and the majority, 79 protocols (78.2%), utilise a combination of more than three databases.

2.6 Origin of the Systematic Review

A total of 30 countries contributed to the registration of systematic review protocols on the detection of oral cancer. A bar diagram (Fig. 1) illustrates the geographical distribution of these systematic review protocols by country. India leads with the highest number of registrations (31, 26.27%), followed by Brazil (14, 11.86%), China (7, 5.93%), Spain (6, 5.08%), and Italy (6, 5.08%). Eleven countries registered only one systematic review. Regarding collaborative research, 13 of the systematic reviews involved international collaborations, while the remaining 88 were affiliated with a single country. India, Brazil, and the USA had the most collaborative reviews, with three each.

2.7 Affiliated institutions

A total of 84 institutions contributed to the registration of systematic review protocols on the detection of oral cancer. The top 15 most productive institutions are listed in Table 6. Santiago de Compostela University in Spain ranks first, with 5 protocol registrations. KLE VK Institute of Dental Sciences and Research in India holds second place with 4 protocols. The University of São Paulo in Brazil and the University of Foggia in Italy are tied for third place, each registering 3 protocols. Additionally, 11 institutions share the fourth rank, each having registered 2 protocols.

2.8 Interventions

Among the selected systematic reviews protocols, almost all (99.0%) reported interventions, with only one (1.0%) not doing so. The interventions, listed by frequency in Table 7, show that biomarkers were the most common, appearing in 16 protocols (13.4%). Other frequently reported interventions included oral cancer screening in 13 protocols (10.9%), artificial intelligence in 12 (10.1%), vital staining and miRNAs in 7 protocols each (5.9%), and both biopsy and deep learning in 6 protocols each (5.0%). Histopathology was reported in 5 protocols (4.2%), while DNA methylation, human papillomavirus, and chemotherapy were each found in 4 protocols (3.4%). Radiotherapy and cell phone applications were mentioned in 3 protocols (2.5%), and computer neural networks and immunohistochemistry in 2 protocols each (1.7%). Additionally, 25 other interventions were reported once each.

Discussion

Registering a systematic review protocol ensures authors may track the study from data collection to the final review, ensuring transparency throughout the review process (A Booth et al., 2020). It plays an essential role in reducing potential biases (Chandler, Cumpston, Li, Page, & Welch, 2019; Davies, 2012). The methodological details outlined in a protocol should be available in the public domain to help

promote transparency and accountability, reduce duplication, improve collaborative opportunities, facilitate peer review, and enhance credibility (Allers, Hoffmann, Mathes, & Pieper, 2018; Ruano et al., 2018; Sideri et al., 2018). Protocol registration also allows the scholarly community to monitor the progress of the systematic review. Some publishers also recommend or require protocol registration as part of their guidelines. This study is the first to use PROSPERO data to perform a protocol analysis of systematic reviews on the detection of oral cancer.

Several well-known registries exist to put protocols into the public domain. However, PROSPERO is the only free, open-access registry, making it a single searchable source of protocols for ongoing and completed reviews.

This analysis highlights a significant increase in systematic review protocols on the detection of oral cancer, with minor fluctuations over time (2014–2024). Registration rates have been higher in the last five years than in the first. Some factors may have contributed to this rise. Oral cancer, or oral squamous cell carcinoma, poses a major global health concern, ranking as the 16th most common cancer worldwide, 12th among men, and 18th among women. And it holds the 15th rank in mortality (Warnakulasuriya, 2009; WHO, 2022). Recognised as a global health issue, early detection and diagnosis are crucial; they have led to advanced research studies that could be a reason for the increase in systematic review registrations.

Systematic reviews are the most reliable, comprehensive, and popular method. They involve systematically identifying, synthesizing, and evaluating all available evidence to provide a strong, empirically derived answer to a specific research question (Patole, 2021). This could be another reason for the rising registration of systematic review protocols. Over the years, the number of funded research projects or those supported by funding agencies has significantly increased. Most funded systematic reviews have been registered in the past five years. Most of this funding comes from highly prolific universities, ministries, state organizations, and research projects. This strong support from prominent funding agencies may contribute to the rise.

The first protocol on oral cancer detection was registered in 2014, with only one registration that year. The low registration in the early years may be due to limited awareness of protocol registration and the initial phase of PROSPERO.

As of August 8, 2024, according to PROSPERO, only 8 registered systematic review protocols had reached their expected completion date, with just 5 published. Of the 101 registered protocols, 90.3% (n = 93) remain ongoing. To verify the accuracy of PROSPERO's status, we searched the titles of these systematic reviews in the PubMed and Scopus databases and found that 30 registered protocols had been published. This indicates that many authors did not update the status of their reviews in PROSPERO after initial registration. The low completion rate may also be attributed to early-stage challenges such as insufficient data, difficulties in data collection methods, limited database availability, unrealistically short expected completion times, and possibly personal factors (Zhang, Gao, Xie, Lian, &

Tian, 2021). Evaluating and tracking progress on time is vital to avoid these problems in future research. Proper planning and adhering to the schedule will help ensure the research is completed as expected.

The report on data retrieval databases reveals that nearly 99% of systematic review protocols (100) utilise PubMed for data retrieval. Compared to other most-used databases such as Scopus, Web of Science, Embase, and the Cochrane Library, PubMed's free accessibility may be a key factor contributing to its high usage rate. Other factors include PubMed's comprehensive medical and biomedical literature coverage, standardised indexing, advanced search tools like Medical Subject Headings (Mesh), and search operators. PubMed's emphasis on quality and relevance, integration with NIH resources, and frequent updates may contribute to its usage rate (Falagas, Pitsouni, Malietzis, & Pappas, 2008). Only two systematic review protocols relied solely on PubMed, while the rest used a combination of databases. Using multiple databases helps reduce publication bias, provides broader coverage, and improves search precision. These advantages make systematic reviews more comprehensive, accurate, and reliable (Bramer, Rethlefsen, Kleijnen, & Franco, 2017). Reporting search strategies is essential in protocol registration, yet only 41 (40.6%) of systematic reviews included this information, while the remainder did not. This may be due to a lack of awareness or the complexity involved in reporting.

All selected systematic review protocols reported assessing risk of bias, though 8 did not specify the tools they used for this assessment. Since bias can lead to misleading conclusions, evaluating it is essential to identify high-quality evidence. The most used tools are QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) (32%), the Newcastle-Ottawa Scale (NOS) (19%), and the Cochrane Risk of Bias (RoB) Tool (8.8%). Each tool addresses specific study designs and biases, contributing to a more robust and rigorous systematic review process.

Systematic reviews require managing large datasets from numerous studies, and data analysis software greatly simplifies data extraction, organization, and analysis. By automating these tasks, the software reduces manual effort and human error (Gurevitch, Koricheva, Nakagawa, & Stewart, 2018). 34 studies reported that the data analysis software RevMan (Review Manager), STATA, R packages, and SPSS are the tools most used for statistical analysis, effect size calculation, forest plot creation, and conclusion. However, 35 studies did not report data synthesis methods, and 67 did not report data analysis software. This high rate of non-reporting on synthesis methods and analysis tools impacts the reproducibility and transparency of the research.

Based on country-wise and institution-wise participation, 30 countries and 84 institutions contributed to the registered systematic review protocols. India leads with the highest number of registrations, approximately 26.27% of the systematic reviews, followed by Brazil (11.86%) and China (5.93%). Among the systematic review protocols, 13 involved multi-country collaboration, with India, Brazil, and the USA having the most collaborations. India also has the highest number of institutional contributions, with 22 Indian institutions involved. Santiago De Compostela University in Spain holds the highest individual registration. Table 6 highlights the top 15 contributing institutions, strongly representing Indian institutions. This prominence is primarily due to India's high incidence of oral cancer. According to Global

Cancer Observatory data, Asia shows high rates of oral cancer, with an incidence rate of 66.3%, a mortality rate of 75.1%, and a prevalence rate of 62.4%. India has the highest rates of both incidence and mortality for oral cancer among men and women. The disease primarily impacts the Indian population, where lifestyle factors such as tobacco use, alcohol consumption, and betel quid chewing contribute to the elevated incidence rates (Gupta & Johnson, 2014; Warnakulasuriya, 2009). The prevalence of oral cancer as a public health issue in India likely increases the demand for significant research and development in this field.

One systematic review protocol did not report the intervention methods, while the remaining 100 systematic review protocols did. The top three intervention methods are the use of biomarkers, oral cancer screening, and artificial intelligence. Various intervention methods are employed to detect oral cancer early, essential for effective treatment and improved survival rates. Certain systematic reviews investigated the same interventions and reported similar outcomes. Researchers should strengthen communication and foster scholarly networks across countries and institutions to prevent redundant research and resource wastage.

Conclusion

This study examines registered protocols of systematic reviews for detecting oral cancer in the PROSPERO registry. It finds a low completion rate among these systematic reviews. India had the highest number of registrations, with 5 Indian-affiliated institutes listed among the 15 most productive institutes. This analysis suggests that systematic reviews require strong institutional collaborations within a country and internationally. Such collaborations could help prevent the repetition of the same themes and reduce duplication, ultimately leading to a more efficient use of scientific and economic resources. Protocol registration makes research themes and methodologies publicly available and accessible. However, incomplete protocols may also result in wasted time. In this study, 59.8% of registrations did not report data analysis software, 35% did not report data synthesis methods, 59.4% did not report the search strategy, and 1% did not report interventions. More attention should be paid to ensuring full data reporting, and there is a need for a standardized system to address this issue.

Declarations

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Competing interests

The authors declared no potential conflicts of interest regarding this article's research, authorship, and/or publication.

Ethics approval

Ethics approval is not required for this study because the data analyzed is sourced from the PROSPERO database, which is publicly available.

Data availability statement

The datasets used and analysed during the current study are available from the corresponding author and study investigators upon reasonable request.

Disclosure of use of Generative AI

No AI tools were used to generate scientific content or interpret the study findings.

CRediT Author contributions

All authors met the ICMJE criteria, and all those who fulfilled these criteria are listed as authors.

AK: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization Writing – original draft.

AKN: Supervision, Validation, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.

All authors contributed to the preparation, review, and approval of the final manuscript

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Tables

Tables 1 to 7 are available in the Supplementary Files section.

Figures

Figure 1 Country-wise production of systematic review protocol

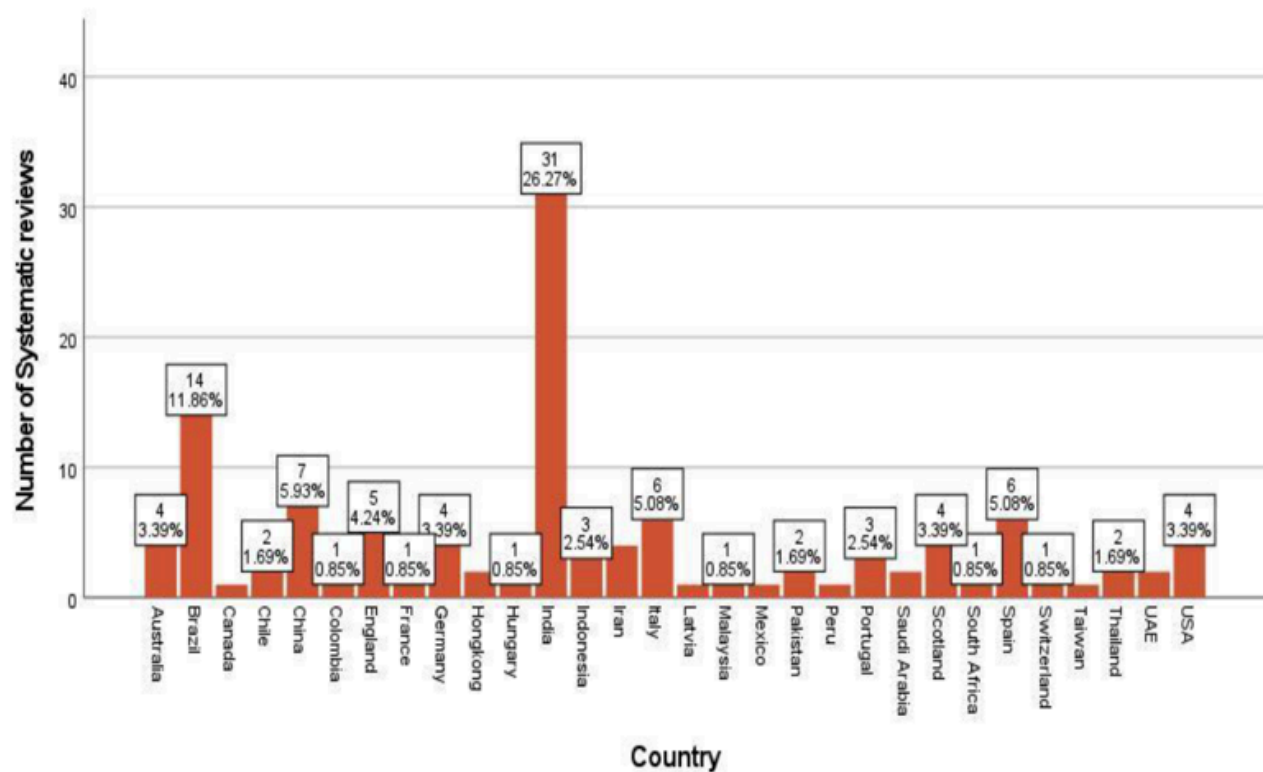


Figure 1

See image above for figure legend

Supplementary Files

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