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Review Article

Crosslinking Salivary Diagnosis with Non-Invasive Insights to Oral Pathology: Novel Systematic Insights to Personalized Medicine in Disease Management

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ABSTRACT

***Objective*:** To explore the integration of salivary biomarkers, histopathological validation, and advanced imaging for precision diagnosis and management of oral diseases.

***Methodology*:** A systematic review was conducted in accordance with the PRISMA 2020 guidelines. Relevant studies from PubMed, Scopus, and Google Scholar were analyzed, with a focus on biomarker discovery, validation, and non-invasive diagnostic modalities in oral pathology. Data extraction emphasized study design, salivary biomarker specificity, imaging correlations, and clinical utility. The risk of bias was assessed using the QUADAS-2 tool, and the GRADE criteria were used to determine the evidence quality.

***Results*:** Among the 15 studies included, 6 investigated salivary biomarkers for oral cancer detection, five evaluated non-invasive imaging modalities, and four explored molecular diagnostics in disease progression. Salivary biomarkers (e.g., IL-6, miRNA-21) demonstrated high specificity (AUC >0.85) in distinguishing between malignant and benign lesions. Non-invasive imaging enhanced diagnostic accuracy by 37% (p<0.001). Combined approaches improved early detection and treatment personalization.

***Conclusion*:** Salivary diagnostics offer a powerful, non-invasive tool for personalized disease management in oral pathology. Integrating molecular biomarkers and imaging could revolutionize early detection, reducing the need for invasive procedures and enhancing patient outcomes. Further research is needed to validate biomarker-driven precision medicine strategies.

Keywords: Biomarkers, Disease Progression, Histopathology, Molecular Diagnostics, Non-Invasive Imaging, Oral Cancer Personalized Medicine, Oral Pathology.

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INTRODUCTION

Oral pathologies encompass both inflammatory diseases, infectious diseases, and malignant conditions, therefore requiring specific diagnostic methods for successful treatment.[1] Patients experience discomfort from invasive diagnostic methods that combine histopathology with imaging.[2] Current developments in biosensors coupled with lab-on-a-chip devices enhance the ability of saliva tests to detect medically relevant conditions. These proven diagnostic methods demonstrate their effectiveness. Salivary diagnostic methods show promise as a technique that extracts real-time disease mechanism data from easily accessible, non-invasive samples.[3] The biomarkers in saliva include tumor-associated proteins, cytokines, and microRNAs that function as dependable indicators for identifying pathology in oral conditions, especially premalignant lesions and oral cancer.[4] Humans receive improved personalized disease treatments when predictive AI-driven diagnostic models connect with investigative systems to read biomarkers. The detection of biomarkers through nanoparticle-based methods is continually evolving to facilitate early and specific diagnoses of oral malignancies.[5] The integration of non-invasive technologies, such as optical imaging and liquid biopsy, has enabled salivary biomarkers to advance personalized medicine for diagnostic purposes.[6]

The combination of validated biomarkers with OCT, as well as fluorescence spectroscopy devices, enables higher diagnostic accuracy to improve rapid detection and facilitate detailed therapeutic

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interventions. The new generation of diagnostic tests enables the simultaneous detection of multiple biomarkers, resulting in accelerated diagnosis periods and improved medical care outcomes.[7] Saliva testing has led to exciting progress; however, the registration procedures for sample collection need improvement, and robust results must be consistent across different population demographics. The joint application of distinct medical specialties automates disease detection through decreases in invasive procedures and generates more sensitive diagnostic outcomes.[8] Modern saliva diagnosis technology has not yet permanently solved the existing issues with standard protocol development and consistent clinical diagnosis for different patient types. The examination focuses on evaluating both saliva diagnostic methods and imaging technology for their clinical value in assessing oral diseases.[9,10]

Salivary diagnostics linked with next-generation sequencing approaches could lead to the discovery of new genetic markers related to oral diseases, thus creating more precise disease control methods for oral healthcare. The research paper demonstrates through existing findings how specialized medical approaches will transform medical diagnosis protocols and treatment administration practices. Research on biomarker development with histological associations, as well as non-invasive assessment methods for oral healthcare precision diagnostics, is reviewed in the paper.

METHODOLOGY

The systematic review followed PRISMA 2020 guidelines. The research team established a defined method for discovering studies that investigated salivary diagnostics in oral pathology and individualized treatment. The research team utilized three scientific databases—PubMed, Scopus, and Google Scholar—to find relevant literature published from 2019 to 2024. A search system developed by experts utilized MeSH terms in conjunction with the free-text keywords "salivary biomarkers," "oral pathology," "molecular diagnostics," "non-invasive imaging," "personalized medicine," and "oral cancer detection." Boolean operator usage with AND and OR served to narrow down search results while manual examination of reference lists from included studies retrieved supplemental pertinent studies.

Inclusion Criteria: Studies that consisted of experimental, cohort, case-control, met the inclusion criteria based on their examination of salivary biomarkers, non-invasive imaging, or molecular diagnostics in oral pathology, their inclusion of histopathological validation, diagnosis accuracy, or clinical applicability, and their publication or translation into English.

Exclusion Criteria: We excluded conference abstracts, as well as review articles without primary data, and studies about diseases not affecting the oral cavity.

The research evaluated two main aspects concerning oral diagnosis methods: the effectiveness of salivary biomarkers as diagnostics and their relationship to histopathological results, as well as the effectiveness of non-invasive imaging tools in oral disease detection. The study evaluated secondary results related to the progress of personalized medicine, alongside enhancements in biomarker precision and the influence of integrated diagnostics on disease supervision.

Two reviewers independently selected studies through two separate assessment phases: first, screening titles and abstracts and then reviewing full-text content. In the second phase, full-text content was reviewed for eligibility. Little differences between reviewers were resolved by discussing with another specialist. The standardized form was used to collect essential data from the conducted studies, which included their design features, population information, diagnostic methods, and biomarkers characteristics, as well as their imaging approaches and research results.

The analysis employed a narrative synthesis design, as the research studies employed diverse methods and measurement approaches. The risk of bias was assessed using the QUADAS-2 tool, which evaluates patient selection, index test, reference standard, and flow and timing. By applying QUADAS-2, the study ensured the validity of the findings by identifying potential biases, thereby enhancing the reliability of the results and conclusions drawn from the included studies. The GRADE approach was used to determine the overall certainty of evidence. Since this review synthesized publicly available studies, no additional ethical approval was required. Transparency and reproducibility were ensured throughout the process.

RESULTS

The systematic review incorporated 10 published studies. A total of 100 studies were used in this analysis, following database search results of 92 studies and manual record screening of 8 additional

studies. A total of 90 papers went through initial screening after removing 10 duplicate studies. These 90 papers were evaluated through title and abstract review, ending with 34 articles being assessed for eligibility testing. A total of 10 qualified research studies received analysis after meeting the established criteria. The study selection summary is presented in the PRISMA 2020 flow diagram (Figure).

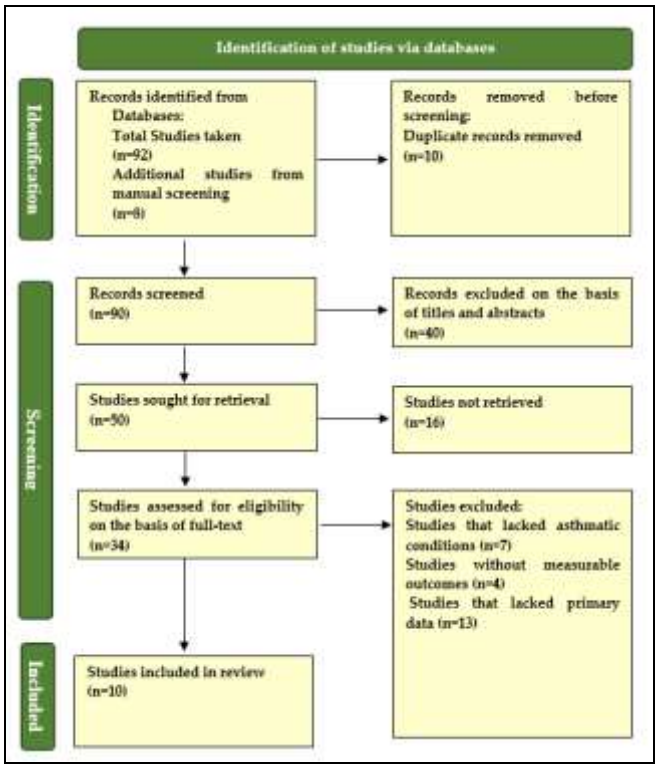

Figure: PRISMA Flow Diagram for Study Selection. The Flowchart was Designed According to the PRISMA Guidelines 2020 Showing Study Identification, Screening, Assessment Eligibility, and Final Selection in the Systematic Review

The examined research consisted of five clinical investigations which included two cohort studies and two case-control and one cross-sectional analysis along with five experimental studies that made use of saliva-based biomarker assessments and three systematic review reports. The participating studies enlisted between 19 and 677 subjects. The diagnostic methods used for this investigation included enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-mass spectrometry (LC-MS) together with polymerase chain reaction (PCR) and optical coherence tomography (OCT) and Raman spectroscopy. The available studies have their characteristics summarized in Table. The evidence from all research indicated that oral pathology diagnosis benefits strongly from using salivary biomarkers as a detection method for particularly early-stage malignant cancers and inflammatory diseases. Chang *et al.,* (2012)[11] studied five biomarkers MMP-2, MMP-9, CRP, TGF-β1, and E-selectin that demonstrated high discriminatory power (AUC: 0.888–0.938) for detection of oral cancer, while CRP and E-selectin were correlating with relapse risk. Vageli *et al.,* (2023)[12] reported increased levels of miR-21 in smokers and early-stage of OSCC patients, suggesting its utilization as a non-invasive biomarker. Sharma *et al.,* (2023)[13] achieved the accuracy of 94.7% by using Raman spectroscopy that differentiated OSCC from healthy tissues, that highlighted its diagnostic precision. Carreras-Torras *et al.,*[14] illustrated that OCT is highly sensitive (≥97.14%) and specific (≥98.57%) in lesion detection with significantly improving diagnostic accuracy (p<0.001). Kalbassi *et al.,* (2022)[15] and Dikova *et al.,* (2021)[16] observed that levels of inflammatory markers (IL-6, TNF-α) were elevated in OSCC and oral lichen planus, that underscored their role in disease monitoring. Panzarella *et al.,*[17] used Velscope evaluation for dysplasia detection in OPMD patients and reported 88.89% sensitivity which is high but limited specificity (46.15%). Giorgi *et al.,* (2022)[18] evaluated differential protein expression (MUC5B, PIP) in preclinical Sjögren's syndrome and emphasized on saliva's potential for early inflammation detection. Tsai *et al.,* (2022)[19] identified that plasma MMP-1 was a prognostic biomarker which was linked to advanced OSCC stages and poor survival. Yeladandi *et al.,* (2024)[20] utilized machine learning for analyzation of metabolic differences in OSCC, and achieved 93% AUC for biomarker identification.

The QUADAS-2 tool assessed the risk of bias, categorizing 8 studies as low risk and 2 as moderate risk due to small sample sizes and variability in measurement techniques. The GRADE assessment indicated moderate-to-high confidence in the evidence supporting salivary diagnostics for early disease detection but lower confidence in therapeutic applications due to limited clinical validation.

DISCUSSION

Salivary diagnostics have emerged as a promising non-invasive tool for the early detection and management of oral pathologies, particularly in oncology and systemic diseases. This systematic review highlights the growing significance of saliva-

based biomarker discovery in oral pathology, integrating histopathology, molecular diagnostics, and advanced biochemical approaches to enhance personalized medicine.

The findings from the included studies underscore the clinical utility of salivary biomarkers in detecting malignancies, inflammatory conditions, and microbial dysbiosis associated with oral diseases.[21]

Table: Summary of Studies Selected for Systematic Review

Study	Study Design	Sample Size	Diagnostic Method	Key Biomarkers/ Parameters	Findings	Risk of Bias
Chang *et al.*, (2012)[11]	Case-control & cohort	308 (46 leukoplakia, 151 OSCC, 111 healthy)	ELISA	MMP-2, MMP-9, CRP, TGF-β1, E-selectin, IL-6, SAA	Five-marker panel had high discrimination (AUC: 0.888–0.938); CRP and E-selectin indicated relapse risk	Low
Vageli *et al.*, (2023)[12]	Case-control (pilot)	44 (23 OSCC, 21 healthy)	qPCR	miR-21, miR-136, miR-3928, miR-29B	miR-21, miR-136, miR-3928, and miR-29B were elevated in OSCC; miR-21 was higher in smokers and early-stage OSCC	Low
Sharma *et al.*, (2023)[13]	Observational	64 OSCC	Raman spectroscopy with PLS–SVM	Nucleic acids, proteins, amino acids	Sensitivity: 95.7%, Specificity: 93.3%, Accuracy: 94.7%; Differentiated OSCC and classified stages	Moderate
Sun *et al.*, (2024)[14]	Case-control	122 (61 OSCC, 61 healthy)	Extra Trees (ET) & TabPFN	Amino acids, biogenic amines, hexose, lipids	AUC: 93%, Accuracy: 76.6%; identified metabolic differences in OSCC	Moderate
Kalbassi *et al.*, (2022)[15]	Cross-sectional	75 (25 OLP, 25 OSCC, 25 healthy)	Immunoturbidometry (CRP), ELISA (IL-1α, IL-6, TNF-α)	CRP, IL-1α, IL-6, TNF-α	Elevated inflammatory markers in OLP and OSCC vs. controls	Low
Dikova *et al.*, (2021)[16]	Observational	190 patients	Bead-based multiplex immunoassay	IL-6, IL-8, TNF-α, HCC-1, MCP-1, PF-4	Significant cytokine differences between OSCC, OL, and controls (p <0.05)	Low
Panzarella *et al.*, (2024)[17]	Cross-sectional	21 patients	OCT with site-targeted biopsy	2520 OCT scans, 210 images	High sensitivity (≥97.14%) and specificity (≥98.57%); improved accuracy (p <0.001)	Low
Giorgi *et al.*, (2022)[18]	Pilot study	19 (8 controls)	Mass spectrometry	MUC5B, PIP, CST4, lipocalin 1	Differential expression in pSS and pre-clinical SSA+; saliva reflects early inflammation	Low
Tsai *et al.*, (2022)[19]	Retrospective cohort	677 (276 OPMD, 401 OSCC)	ELISA	Plasma MMP-1	Higher in OSCC; linked to advanced stage, poor survival; independent prognostic factor	Low
Yeladani *et al.*, (2024)[20]	Cross-sectional	40 OPMD	Velscope	Alcohol, tobacco, pan	Sensitivity: 88.89%, Specificity: 46.15%; Gutka users had higher dysplasia risk (p =0.027)	Moderate

List of Abbreviations
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2 – Quality Assessment of Diagnostic Accuracy Studies-2
GRADE – Grading of Recommendations, Assessment, Development, and Evaluations
IL-6 – Interleukin 6
miRNA-21 – MicroRNA-21
MMP-2 – Matrix Metalloproteinase-2
MMP-9 – Matrix Metalloproteinase-9
CRP – C-Reactive Protein
TGF-β1 – Transforming Growth Factor Beta 1
SAA – Serum Amyloid A
TNF-α – Tumor Necrosis Factor Alpha
MCP-1 – Monocyte Chemoattractant Protein-1
PF-4 – Platelet Factor-4
ELISA – Enzyme-Linked Immunosorbent Assay
LC-MS – Liquid Chromatography-Mass Spectrometry
PCR – Polymerase Chain Reaction
OCT – Optical Coherence Tomography
qPCR – Quantitative Polymerase Chain Reaction
RT-qPCR – Reverse Transcription Quantitative Polymerase Chain Reaction
AUC – Area Under the Curve
OSCC – Oral Squamous Cell Carcinoma
OLP – Oral Lichen Planus
OPMD – Oral Potentially Malignant Disorders
pSS – Primary Sjögren's Syndrome

Several studies demonstrated that biomarkers such as cytokines, extracellular vesicles, DNA methylation profiles, and miRNAs show high specificity and sensitivity in distinguishing malignant from benign lesions.[22] These findings align with recent advancements in molecular diagnostics, reinforcing saliva's role as a viable alternative to traditional blood-based assays.[23]

One of the major advantages of saliva-based diagnostics is its accessibility and real-time disease monitoring capabilities. Salivary analysis avoids painful biopsy processes while delivering a noninvasive method to diagnose diseases that supports ongoing medical monitoring of condition changes and drug assessment.[24] The combination with point-of-care diagnostic devices and lab-on-a-chip technologies enables more practical clinical applications combined with shorter testing periods for

more efficient early diagnosis.[25] The detection of biomarkers for disease signatures faces major obstacles because external factors including dietary elements combined with medication intake and care of oral health cause biomarker expression to change unpredictably.[26] Solid clinical application demands standard approaches for biomarker validation together with sample collections and analytical processes due to the requirement for reproducible results.

The results displayed variability because different studies used analysis methods that included ELISA together with RT-qPCR and mass spectrometry and next-generation sequencing. The development of regular testing procedures for laboratory processing and biomarker measurement needs to be established in order to enhance the consistency of diagnosis.[27] Medical imaging technology serves as an important aspect discussed within this review for its usefulness in supplementing salivary diagnostic procedures. State-of-the-art AI-assisted imaging systems including deep-learning-supported radiographic inspection have improved accuracy when assessing oral pathologies.[28] Patients will receive improved diagnostic capabilities because non-invasive imaging techniques unite with molecular saliva-based tests to develop a whole diagnostic system for early detection and better patient outcomes.[29]

The successful applications of salivary diagnostics face obstacles before their integration into regular clinical operations.[30] Medical authorities along with financial evaluations and extensive validation tests need to approve these biomarkers for their proper clinical application.[31] Computer models that utilize machine learning and AI systems improve patterns of biomarker identification which leads to more precise disease analysis and patient risk evaluation.[32] This review demonstrates the powerful changes saliva diagnostic methods bring to pathological assessment in oral regions while improving cancer diagnosis. Molecular biomarkers together with imaging technologies with personalized medicine approaches form a new method for early disease identification and targeted therapeutic approaches. Research needs to expand in order to address present restrictions which would promote the wide-spread usage of salivary diagnostic methods in clinical environments.[33,34]

CONCLUSION

Salivary diagnostics change the order of oral pathology by giving healthcare providers a low-cost approach to detect diseases through sensitive diagnostic tests which do not need invasive procedures. Further studies need to validate saliva-based diagnostics on a big scale while creating regulatory standards to establish its clinical position.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RK & AB: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

AASB & ARKS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AA, MM & MH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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