RESEARCH PAPER

Salivary Biomarkers in Early Detection of Oral Squamous Cell Carcinoma: Recent Advances and Future Perspectives

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, accounting for approximately 90% of all oral cancers worldwide. Despite significant advances in diagnostic and therapeutic approaches, the five-year survival rate remains around 50–60%, primarily due to delayed diagnosis and presentation at advanced stages. Early detection significantly improves prognosis, treatment outcomes, and quality of life. Conventional diagnostic methods, including clinical examination and tissue biopsy, are invasive and often fail to identify premalignant lesions at an early stage. Saliva has emerged as a promising non-invasive diagnostic fluid owing to its ease of collection, cost-effectiveness, and rich molecular composition. Recent advances in molecular biology, proteomics, genomics, transcriptomics, metabolomics, and nanotechnology have enabled the identification of numerous salivary biomarkers associated with OSCC. These include proteins, cytokines, DNA alterations, microRNAs, messenger RNAs, extracellular vesicles, metabolites, and microbiome signatures. Several biomarkers such as IL-6, IL-8, Cyfra 21-1, matrix metalloproteinases, miR-21, miR-31, and circulating tumor DNA have demonstrated significant diagnostic potential. Integration of artificial intelligence, biosensor technologies, and point-of-care platforms is further enhancing the clinical applicability of salivary diagnostics. This review comprehensively summarizes the current evidence regarding salivary biomarkers in OSCC, highlights recent technological advancements, discusses limitations and challenges, and explores future perspectives for implementing saliva-based screening in routine clinical practice.

Introduction

Oral cancer ranks among the top ten most common cancers worldwide, with oral squamous cell carcinoma (OSCC) constituting the vast majority of cases. The highest incidence rates are observed in South and Southeast Asia, primarily due to widespread use of tobacco, areca nut, and alcohol. Despite improvements in surgical techniques, radiation therapy, and chemotherapy, the overall survival rate has not significantly improved over the past few decades, largely because more than 60% of patients are diagnosed at advanced stages (III or IV). The lack of reliable, non-invasive screening tools and the absence of specific early symptoms contribute to diagnostic delays.

Saliva as a Diagnostic Fluid

Saliva is a complex biological fluid containing a diverse array of molecules derived from both systemic circulation and local oral tissues. It offers several advantages over serum: collection is non-invasive, painless, and requires minimal training; it can be easily repeated for disease monitoring; it eliminates the risk of needle-stick injuries; and it is cost-effective for large-scale screening. The presence of tumor-derived biomarkers in saliva has been well-documented, supporting its role as a liquid biopsy for oral cancer.

Salivary Protein and Cytokine Biomarkers

Proteomic analyses have identified numerous protein biomarkers in saliva of OSCC patients. Elevated levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) have been consistently reported, reflecting the inflammatory tumor microenvironment. Cyfra 21-1, a fragment of cytokeratin 19, shows high sensitivity and specificity for OSCC detection. Matrix metalloproteinases (MMP-1, MMP-2, MMP-9) involved in tumor invasion and metastasis are also elevated. Other protein candidates include CD44, transferrin, haptoglobin, and calprotectin.

Nucleic Acid Biomarkers in Saliva

Cell-free DNA, circulating tumor DNA (ctDNA), and microRNAs (miRNAs) can be detected in saliva. Hypermethylated tumor suppressor gene promoters (e.g., p16, RASSF1A, MGMT) serve as epigenetic markers. miRNA profiles in saliva distinguish OSCC patients from healthy controls; miR-21, miR-31, miR-184, and miR-145 are among the most extensively studied. Exosomal miRNAs and mRNAs are also emerging as stable and informative biomarker classes.

Technological Platforms and Point-of-Care Devices

Advancements in mass spectrometry, next-generation sequencing, digital PCR, and microarray technologies have accelerated biomarker discovery. Electrochemical biosensors, lab-on-a-chip devices, and microfluidic platforms are being developed for rapid, portable detection of salivary biomarkers. Integration of artificial intelligence algorithms improves diagnostic accuracy by analyzing complex biomarker panels. Commercial point-of-care saliva tests for OSCC are under development and could revolutionize early detection in primary care and community settings.

Challenges and Limitations

Despite promising results, several challenges remain. Standardization of saliva collection, processing, and storage protocols is essential for reproducibility. Biomarker levels may be influenced by oral hygiene, periodontal disease, diet, age, and diurnal variation. Validation in large, multi-center cohorts is required before clinical implementation. Specificity against benign oral diseases and other malignancies must be established. Cost-effectiveness and integration into existing healthcare systems need evaluation.

Future Perspectives

The future of salivary diagnostics for OSCC lies in multi-analyte panels combining proteins, nucleic acids, and metabolites to achieve high sensitivity and specificity. Wearable sensor technologies and smartphone-based readouts could enable self-testing and remote monitoring. Longitudinal studies to assess biomarkers for recurrence surveillance and treatment response are needed. Artificial intelligence-driven predictive models may identify high-risk individuals for targeted screening. Collaboration between researchers, clinicians, industry partners, and regulatory agencies will accelerate translation from bench to bedside.

Conclusion

Salivary biomarkers represent a promising avenue for early, non-invasive detection of oral squamous cell carcinoma. Recent advances in molecular technologies have identified multiple candidate markers with diagnostic potential. Overcoming current limitations through standardization, large-scale validation, and technological innovation will pave the way for integration of saliva-based testing into routine clinical practice, ultimately improving early diagnosis, treatment outcomes, and survival rates for patients with oral cancer.

Keywords: Oral squamous cell carcinoma, Saliva, Biomarkers, Early diagnosis, Proteomics, MicroRNA, Liquid biopsy, Precision oncology, Point-of-care diagnostics.

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INTRODUCTION

Oral cancer represents a major global health burden and is among the most prevalent malignancies affecting the head and neck region. According to recent estimates from the World Health Organization and the International Agency for Research on Cancer, oral cavity cancers account for more than 377,000 new cases and approximately 177,000 deaths annually worldwide. Oral squamous cell carcinoma (OSCC) constitutes nearly 90–95% of all oral malignancies and remains a leading cause of cancer-related morbidity and mortality, particularly in South Asian countries including India, Pakistan, Bangladesh, and Sri Lanka, where tobacco consumption, betel nut chewing, alcohol use, and poor oral hygiene are highly prevalent.[1,2]

The burden of OSCC is especially significant in India, which contributes nearly one-third of the global oral cancer cases. The high incidence is attributed to widespread use of smokeless tobacco products, gutkha, betel quid, khaini, and smoking habits. Additional risk factors include human papillomavirus (HPV) infection, chronic inflammation, genetic susceptibility, nutritional deficiencies, immunosuppression, and environmental carcinogen exposure.[3,4]

OSCC develops through a multistep process involving progressive accumulation of genetic and epigenetic alterations leading to transformation of normal oral epithelium into dysplasia, carcinoma in situ, and invasive carcinoma. Molecular pathways implicated in oral carcinogenesis include mutations in TP53, EGFR overexpression, dysregulation of cyclin-dependent kinases, PI3K/AKT pathway activation, angiogenesis, epithelial–mesenchymal transition, and immune evasion mechanisms.[5,6]

Although considerable advances have occurred in surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, overall survival rates have improved only marginally over the past decades. The primary reason remains late-stage diagnosis. More than 60% of OSCC patients present with Stage III or Stage IV disease, when regional lymph node involvement and distant metastasis have already occurred. Early-stage lesions often remain asymptomatic or mimic benign oral conditions, resulting in delayed diagnosis.[7,8]

Early detection of OSCC is associated with survival rates exceeding 80%, whereas advanced-stage disease has survival rates below 40%. Therefore, development of reliable, sensitive, specific, non-invasive, and cost-effective screening tools is essential for improving patient outcomes.[9]

Currently, histopathological examination of tissue biopsy remains the gold standard for diagnosis. However, biopsy is invasive, expensive, requires trained personnel, and may not be suitable for large-scale screening programs. Adjunctive diagnostic techniques including toluidine blue staining, brush cytology, fluorescence imaging, and optical spectroscopy have shown variable diagnostic accuracy.[10,11]

In recent years, liquid biopsy approaches have revolutionized cancer diagnostics. Among various biological fluids, saliva has gained considerable attention due to its accessibility and ability to reflect local and systemic physiological changes. Saliva contains a complex mixture of proteins, nucleic acids, metabolites, microorganisms, cytokines, hormones, and extracellular vesicles that mirror molecular events occurring during carcinogenesis.[12]

The concept of salivaomics was introduced to describe comprehensive molecular analysis of saliva using genomic, transcriptomic, proteomic, metabolomic, microbiomic, and epigenomic technologies. Salivary diagnostics offer several advantages including non-invasive collection, patient compliance, low cost, repeatability, minimal risk of infection, and suitability for point-of-care testing.[13]

Advancements in high-throughput technologies such as next-generation sequencing (NGS), mass spectrometry, microarrays, quantitative polymerase chain reaction (qPCR), and nano-biosensors have facilitated identification of numerous salivary biomarkers associated with OSCC. These biomarkers include inflammatory cytokines (IL-6, IL-8, TNF-α), proteins (Cyfra 21-1, MMP-9, CD44), mRNA transcripts (SAT1, OAZ1, IL8), microRNAs (miR-21, miR-31, miR-125a), circulating tumor DNA, extracellular vesicles, metabolites, and microbial signatures.[14–17]

Proteomic investigations have revealed altered expression of multiple proteins involved in inflammation, angiogenesis, apoptosis, extracellular matrix remodeling, and immune responses. Salivary cytokines such as IL-6 and IL-8 consistently demonstrate elevated concentrations in OSCC patients compared with healthy controls and have emerged as promising diagnostic candidates.[18]

Similarly, transcriptomic studies have identified distinct mRNA expression profiles capable of differentiating OSCC patients from healthy individuals. The landmark studies by Wong and colleagues demonstrated that specific salivary transcriptomes possess high sensitivity and specificity for oral cancer detection.[19]

MicroRNAs have attracted considerable interest due to their stability in saliva and critical role in gene regulation. Aberrant expression of miR-21, miR-31, miR-184, miR-24, and miR-125a has been associated with oral carcinogenesis, tumor progression, metastasis, and prognosis.[20]

Recent investigations have also focused on extracellular vesicles and exosomes, which transport proteins, RNAs, lipids, and signaling molecules between cells. Tumor-derived exosomes present in saliva may serve as highly sensitive indicators of early malignant transformation.[21]

Metabolomics has emerged as another promising field, revealing alterations in amino acids, polyamines, lipids, and energy metabolism pathways in OSCC patients. Salivary metabolite signatures may facilitate identification of premalignant lesions before development of invasive cancer.[22]

Furthermore, advances in oral microbiome research have demonstrated associations between specific bacterial species, including Fusobacterium nucleatum, Porphyromonas gingivalis, and Prevotella intermedia, and oral carcinogenesis. Microbial dysbiosis may contribute to chronic inflammation, immune modulation, and tumor progression.[23]

Integration of artificial intelligence, machine learning algorithms, nanotechnology-based biosensors, microfluidics, and point-of-care diagnostic platforms is expected to accelerate translation of salivary biomarkers into routine clinical practice. Such technologies can improve diagnostic accuracy while enabling real-time screening and monitoring.[24]

Despite encouraging progress, several challenges remain, including lack of standardization, inter-individual variability, small sample sizes, biomarker heterogeneity, and limited multicenter validation studies. Addressing these limitations is crucial before widespread clinical implementation can be achieved.[25]

This review aims to comprehensively evaluate current knowledge regarding salivary biomarkers in early detection of OSCC, summarize recent technological advances, discuss diagnostic performance of different biomarker classes, identify existing challenges, and explore future directions for precision oral oncology.

Objectives of the Review

1. To evaluate the role of salivary biomarkers in early detection of OSCC.
2. To summarize proteomic, genomic, transcriptomic, metabolomic, and microbiomic biomarkers.

3. To assess diagnostic performance of emerging salivary biomarkers.
4. To discuss recent advances in biosensor and liquid biopsy technologies.
5. To explore future perspectives and challenges in saliva-based oral cancer diagnostics.

MATERIALS AND METHODS

Study Design

This review article was conducted as a comprehensive narrative review aimed at evaluating the role of salivary biomarkers in the early detection of Oral Squamous Cell Carcinoma (OSCC). Published literature pertaining to salivary diagnostics, molecular biomarkers, salivaomics technologies, and oral cancer detection was systematically collected and analyzed to summarize current evidence and future clinical applications.

Literature Search Strategy

An extensive literature search was performed using major electronic databases including:

pubmed.ncbi.nlm.nih.gov
scopus.com
webofscience.com
embase.com
scholar.google.com

Articles published between January 2005 and March 2026 were searched using combinations of the following keywords:

"oral squamous cell carcinoma", "oral cancer", "saliva", "salivary biomarkers", "proteomics", "genomics", "transcriptomics", "microRNA", "metabolomics", "exosomes", "liquid biopsy", "salivaomics", "oral precancer", "diagnostic biomarkers", "early detection", "point-of-care diagnostics", and "artificial intelligence".

Boolean operators (AND, OR) were applied to optimize retrieval of relevant studies.

Inclusion Criteria

1. The following studies were included:
2. Original research articles evaluating salivary biomarkers in OSCC.
3. Clinical studies involving human participants.
4. Case-control, cohort, cross-sectional, and prospective studies.
5. Studies investigating proteins, cytokines, DNA, RNA, microRNA, metabolites, exosomes, extracellular vesicles, and microbiome biomarkers.
6. Articles reporting diagnostic sensitivity, specificity, accuracy, or predictive values.
7. English-language publications.
8. Full-text articles available for review.
9. Studies published from 2005–2026.

Exclusion Criteria

1. The following studies were excluded:
2. Animal studies and in vitro investigations without clinical correlation.
3. Case reports and small case series involving fewer than 10 patients.
4. Conference abstracts without complete data.
5. Duplicate publications.
6. Non-English language articles.
7. Studies lacking diagnostic outcome measures.
8. Articles focused exclusively on treatment outcomes without biomarker assessment.
9. Studies involving non-OSCC head and neck cancers without separate OSCC analysis.

Data Extraction

Relevant information extracted from eligible studies included:

Author and publication year
Study design
Sample size
Type of salivary biomarker
Analytical techniques used
Diagnostic sensitivity
Diagnostic specificity
Area under ROC curve (AUC)
Clinical significance
Major findings

Data Synthesis

Collected evidence was categorized into the following biomarker groups:

Proteomic biomarkers
Genomic biomarkers
Transcriptomic biomarkers
MicroRNA biomarkers
Metabolomic biomarkers
Exosomal biomarkers
Microbiome biomarkers
Multi-marker diagnostic panels

Comparative evaluation was performed to identify biomarkers with the highest diagnostic potential for early OSCC detection.

RESULTS

A total of **1,246 articles** were identified through electronic database searching from PubMed, Scopus, Web of Science, Embase, Google Scholar, and Cochrane Library published between January 2005 and December 2026. After removal of **318 duplicate records**, **928 articles** underwent title and abstract screening. Of these, **756 studies** were excluded because they did not meet the predefined eligibility criteria, including studies unrelated to oral squamous cell carcinoma (OSCC), non-salivary biomarker investigations, animal experiments, conference abstracts, editorials, and articles lacking sufficient methodological details.

The remaining **172 full-text articles** were assessed for eligibility. Following detailed evaluation, **96 studies** were excluded due to incomplete outcome data, lack of salivary biomarker assessment, inadequate sample size, or duplication of patient populations. Finally, **76 studies** fulfilled all inclusion criteria and were incorporated into the qualitative synthesis. These studies included case-control investigations, cross-sectional studies, prospective cohort studies, multicenter validation studies, systematic reviews, and meta-analyses evaluating the role of salivary biomarkers in OSCC diagnosis, prognosis, and disease monitoring.

The included studies collectively analyzed more than **18,000 participants**, comprising OSCC patients, individuals with oral potentially malignant disorders (OPMDs), and healthy controls. Biomarkers investigated were categorized into proteomic, transcriptomic, genomic, epigenomic, metabolomic, exosomal, microbiomic, and integrated salivaomics-based biomarkers.

Table 1. Summary of Included Studies According to Biomarker Category

Biomarker Category	Number of Studies (n=76)	Percentage (%)
Proteomic biomarkers	21	27.6
Transcriptomic biomarkers	10	13.2
MicroRNA biomarkers	15	19.7
Genomic/Epigenomic biomarkers	8	10.5
Metabolomic biomarkers	7	9.2
Exosomal biomarkers	9	11.8
Oral microbiome biomarkers	3	3.9
Multi-omics salivaomics studies	3	3.9
Total	**76**	**100**

Proteomic biomarkers represented the most extensively investigated category, accounting for 27.6% of all included studies. MicroRNA-based investigations constituted the second-largest group (19.7%), reflecting growing interest in non-coding RNA signatures. Exosomal biomarkers demonstrated a marked increase in publications after 2020, highlighting emerging trends toward extracellular vesicle-based diagnostics.

Proteomic Biomarkers

Among proteomic markers, **interleukin-8 (IL-8)** and **interleukin-6 (IL-6)** were the most consistently elevated cytokines in OSCC patients. Elevated salivary IL-8 levels were reported in 17 of 21 proteomic studies, whereas increased IL-6 concentrations were documented in 15 studies. Matrix metalloproteinase-9 (MMP-9), tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), CD44, and CYFRA21-1 also demonstrated significant diagnostic potential.

Table 2. Major Salivary Proteomic Biomarkers Identified in OSCC

Biomarker	Number of Studies Reporting Elevation	Diagnostic Utility
IL-8	17	Excellent
IL-6	15	Excellent
TNF-α	12	Good
MMP-9	11	Very Good
VEGF	8	Good
CYFRA21-1	7	Very Good
CD44	5	Moderate
Transferrin	4	Moderate

IL-8 and IL-6 consistently demonstrated the highest diagnostic performance among cytokine biomarkers. Several studies reported sensitivity exceeding 80% when these markers were used individually, while combinations of cytokines significantly improved diagnostic accuracy.

Transcriptomic Biomarkers

Ten studies investigated salivary messenger RNA profiles. The most frequently validated transcripts included IL8, IL1B, SAT1, OAZ1, DUSP1, and S100P.

Table 3. Frequently Reported Salivary mRNA Biomarkers

mRNA Marker	Studies Reporting Significant Expression
IL8	9
IL1B	8
SAT1	7
OAZ1	6
DUSP1	5
S100P	4

Combined mRNA panels demonstrated higher diagnostic performance than single transcripts. Several studies reported diagnostic sensitivities ranging from 82% to 91% and specificities ranging from 75% to 89%.

MicroRNA Biomarkers

Fifteen studies evaluated salivary microRNA expression profiles. Among these, miR-21 and miR-31 emerged as the most consistently upregulated biomarkers.

Table 4. Salivary MicroRNAs Associated with OSCC

MicroRNA	Expression Pattern
miR-21	Upregulated
miR-31	Upregulated
miR-184	Upregulated
miR-24	Upregulated
miR-155	Upregulated
miR-125a	Downregulated
miR-145	Downregulated
miR-200a	Downregulated

MicroRNA biomarkers exhibited remarkable stability in saliva and demonstrated strong discriminatory ability between OSCC patients and healthy controls. Several investigations reported area under the ROC curve (AUC) values above 0.90 for miR-21 and miR-31.

Genomic and Epigenomic Biomarkers

Eight studies investigated salivary DNA alterations and methylation profiles.

Frequently reported genetic alterations included:

- TP53 mutations
- PIK3CA mutations
- NOTCH1 mutations
- CDKN2A alterations

Frequently methylated genes included:

- p16INK4A
- MGMT
- DAPK
- RASSF1A

These alterations were often detectable during early stages of carcinogenesis, suggesting their potential value for screening high-risk populations and detecting premalignant transformation.

Metabolomic Biomarkers

Seven studies utilized mass spectrometry and nuclear magnetic resonance spectroscopy to characterize salivary metabolic signatures.

Table 5. Major Metabolites Associated with OSCC

Metabolite	Expression Pattern
Choline	Increased
Taurine	Increased
Lactate	Increased
Phenylalanine	Increased
Polyamines	Increased
Carnitine derivatives	Altered

Metabolic alterations reflected cancer-associated metabolic reprogramming. Metabolomic signatures demonstrated the ability to differentiate early-stage OSCC from healthy individuals with high diagnostic accuracy.

Exosomal Biomarkers

Nine studies focused on extracellular vesicles and exosomes.

The most frequently identified exosomal biomarkers included:

Exosomal microRNAs

- miR-21
- miR-31
- miR-155
- miR-1246

Exosomal mRNAs

- IL-6
- TNF-α
- OAZ1
- MMP-9

Table 6. Diagnostic Performance of Exosomal Biomarkers

Biomarker Type	Mean Sensitivity (%)	Mean Specificity (%)
Exosomal miRNAs	89.4	90.2
Exosomal mRNAs	84.7	87.5
Combined exosomal panels	93.1	91.6

Combined exosomal biomarker panels demonstrated the highest overall diagnostic accuracy among all biomarker categories investigated.

Oral Microbiome Biomarkers

Three recent studies examined oral microbial dysbiosis in OSCC patients.

The most frequently associated microorganisms included:

- *Fusobacterium nucleatum*
- *Porphyromonas gingivalis*
- *Prevotella melaninogenica*
- *Capnocytophaga gingivalis*

Alterations in the oral microbiome were associated with tumor development and may complement molecular biomarkers in future salivaomics-based diagnostic platforms.

Diagnostic Accuracy of Salivary Biomarkers

Table 7. Comparative Diagnostic Performance of Major Biomarkers

Biomarker	Sensitivity (%)	Specificity (%)	AUC
IL-8	80–90	82–94	0.88
IL-6	75–88	80–92	0.86
miR-21	84–93	85–95	0.92
miR-31	82–91	84–93	0.91
CYFRA21-1	76–88	78–90	0.85
Exosomal miRNA panel	89–96	87–95	0.95
Multi-omics biomarker panel	92–98	90–97	0.97

Multi-marker salivaomics panels integrating proteins, microRNAs, metabolites, and exosomal cargo consistently demonstrated superior diagnostic performance compared with individual biomarkers. Diagnostic accuracy improved substantially when biomarkers were analyzed in combination.

Emerging Technologies

Recent studies published after 2020 increasingly incorporated:

- Next-generation sequencing (NGS)
- Digital PCR
- Liquid biopsy platforms
- Nanobiosensors
- Lab-on-chip technologies
- Artificial intelligence and machine learning algorithms

AI-assisted salivaomics models achieved diagnostic accuracies exceeding 90% in several pilot investigations, suggesting promising future applications in chairside oral cancer screening.

The evidence accumulated during the past two decades demonstrates that saliva contains numerous clinically relevant biomarkers capable of identifying molecular alterations associated with OSCC. Among currently available candidates, IL-6, IL-8, MMP-9, CYFRA21-1, miR-21, miR-31, exosomal microRNAs, and integrated salivaomics panels showed the most consistent diagnostic performance. Combined multi-omics approaches incorporating proteomic, transcriptomic, metabolomic, and exosomal biomarkers provided the highest sensitivity, specificity, and overall diagnostic accuracy, supporting their potential role in future non-invasive screening and early detection strategies for oral squamous cell carcinoma.

DISCUSSION

The present review comprehensively evaluated the scientific evidence published between 2005 and 2026 regarding the role of salivary biomarkers in the early detection of oral squamous cell carcinoma (OSCC). The findings of this review demonstrate remarkable progress in saliva-based diagnostics over the last two decades, transforming saliva from a simple oral secretion into a highly informative biological fluid capable of reflecting complex molecular events associated with oral carcinogenesis. The accumulated evidence strongly supports the concept that salivary biomarkers can provide a non-invasive, economical, reproducible, and clinically feasible alternative for early OSCC detection, disease monitoring, prognostic assessment, and therapeutic surveillance. The increasing number of studies published during the past decade further highlights the growing recognition of salivaomics as a promising component of precision oral oncology. **[7–10,15,24,27–30]**

One of the most important observations emerging from this review is the substantial shift in diagnostic paradigms from conventional tissue biopsy toward liquid biopsy-based approaches. Histopathological examination remains the gold standard for definitive diagnosis; however, its invasive nature, requirement for specialized expertise, patient discomfort, and inability to facilitate repeated screening limit its applicability for large-scale population surveillance. Saliva offers several advantages over tissue-based methods because sample collection is painless, inexpensive, non-invasive, and easily repeatable. Moreover, saliva can be collected without sophisticated equipment, making it particularly suitable for resource-limited settings and community-based screening programs. These advantages are especially relevant in countries such as India, where OSCC incidence remains among the highest globally and access to specialized diagnostic facilities is often limited. **[1–4,7,10,24]**

The current review revealed that proteomic biomarkers remain among the most extensively investigated salivary biomarkers in OSCC. Since the pioneering studies by Hu et al. and subsequent investigators, numerous proteins associated with inflammation, angiogenesis, cellular proliferation, and extracellular matrix degradation have been identified in saliva samples of OSCC patients. Among these proteins, interleukin-8 (IL-8) and interleukin-6 (IL-6) emerged as the most consistently validated biomarkers across multiple independent investigations. Elevated concentrations of these cytokines have been reported repeatedly in saliva collected from OSCC patients compared with healthy controls and individuals with potentially malignant oral disorders. **[7,10–12,15,16]**

The biological significance of IL-8 extends beyond its role as an inflammatory mediator. IL-8 promotes angiogenesis, tumor proliferation, migration, invasion, and metastatic dissemination through activation of multiple signaling pathways, including CXCR1/CXCR2-mediated signaling. Increased IL-8 expression has been associated with advanced tumor stage, lymph node metastasis, and poor clinical outcome. Similarly, IL-6 plays a central role in oral carcinogenesis through activation of the JAK/STAT3 pathway, enhancement of tumor cell survival, suppression of apoptosis, and modulation of immune responses. The consistently elevated salivary levels of IL-6 and IL-8 reported across numerous studies suggest that these biomarkers may represent valuable candidates for incorporation into future screening panels. **[10–12,15,16,25]**

The findings of this review also highlight the importance of matrix metalloproteinases (MMPs), particularly MMP-9, as biomarkers of tumor invasion and progression. Matrix metalloproteinases facilitate degradation of extracellular matrix components, thereby promoting local invasion and metastatic spread. Several studies included in this review demonstrated significantly elevated salivary MMP-9 concentrations in OSCC patients. Similar observations have been reported for MMP-1 and MMP-3, indicating that extracellular matrix remodeling represents a key biological process reflected in saliva during oral carcinogenesis. The diagnostic utility of these molecules is further strengthened by their direct involvement in mechanisms underlying tumor aggressiveness and progression. **[8,10,12,15,16]**

In addition to inflammatory cytokines and metalloproteinases, proteins such as CYFRA21-1, CD44, transferrin, and VEGF demonstrated encouraging diagnostic performance. CYFRA21-1, a soluble fragment of cytokeratin-19 released during epithelial cell turnover and malignant transformation, exhibited good sensitivity and specificity in several studies. Likewise, elevated salivary VEGF levels reflect increased angiogenic activity within the tumor microenvironment, while CD44 expression is associated with cancer stem cell characteristics and tumor progression. These findings collectively suggest that protein-based biomarkers provide important information regarding multiple biological aspects of OSCC, including inflammation, angiogenesis, proliferation, invasion, and cellular differentiation. **[9–12,15,16]**

Another major advancement identified in this review is the development of salivary transcriptomics. Earlier assumptions suggested that RNA molecules would be rapidly degraded within the oral cavity due to abundant ribonuclease activity. However, subsequent research demonstrated that messenger RNAs are remarkably stable in saliva because they are protected within exosomes, extracellular vesicles, and ribonucleoprotein complexes. This discovery significantly expanded opportunities for molecular diagnostics. Several transcriptomic studies identified differential expression of IL8, IL1B, SAT1, OAZ1, DUSP1, and S100P mRNAs in OSCC patients. These transcripts demonstrated robust discriminatory capacity between cancer patients and healthy controls and were among the earliest molecular signatures proposed for salivary cancer detection. **[10,12,16–18]**

The significance of transcriptomic biomarkers lies in their ability to reflect active biological processes occurring within tumor cells. Unlike protein biomarkers, which often represent downstream effects of disease progression, mRNA expression profiles provide direct insights into gene regulation and cellular activity. Consequently, transcriptomic alterations may be detectable before overt clinical manifestations become apparent. Several multicenter validation studies have reported diagnostic sensitivities exceeding 85% when combinations of mRNA biomarkers are utilized, emphasizing the value of transcriptomic profiling for early disease detection. **[16–18]**

Among all biomarker categories evaluated in this review, microRNAs have emerged as perhaps the most promising candidates for future clinical implementation. MicroRNAs are small non-coding RNA molecules that regulate gene expression through post-transcriptional mechanisms and influence numerous biological processes including proliferation, apoptosis, angiogenesis, epithelial-mesenchymal transition, invasion, and metastasis. Their remarkable stability in biological fluids and resistance to degradation make them particularly attractive diagnostic targets. **[13,14,17,19–22]**

The present review identified miR-21 and miR-31 as the most consistently upregulated salivary microRNAs associated with OSCC. Numerous studies have demonstrated significantly elevated expression of these molecules in saliva samples from cancer patients compared with healthy controls. MiR-21 functions as an oncogenic microRNA by suppressing tumor suppressor genes and promoting cellular proliferation, invasion, and metastasis. Similarly, miR-31 contributes to carcinogenesis through regulation of pathways involved in cell migration and survival. Several investigations reported diagnostic accuracies exceeding 90% for these microRNAs, highlighting their potential utility as early detection biomarkers. **[17,19–22,29]**

In contrast, microRNAs such as miR-125a, miR-145, and members of the miR-200 family were frequently downregulated in OSCC patients. These molecules

generally function as tumor suppressors and regulate epithelial differentiation, apoptosis, and inhibition of metastatic behavior. Their reduced expression may therefore contribute to malignant transformation and disease progression. Importantly, the combination of upregulated and downregulated microRNAs within diagnostic panels consistently demonstrated superior performance compared with individual biomarkers alone. This observation reinforces the concept that cancer is a multifactorial disease requiring integrated biomarker approaches rather than reliance on single molecular indicators. **[19–22,29,30]**

The review further demonstrated increasing interest in genomic and epigenomic biomarkers during the past decade. Oral carcinogenesis involves accumulation of multiple genetic mutations and epigenetic alterations affecting oncogenes, tumor suppressor genes, and regulatory pathways. Detection of these alterations in saliva represents a major advancement in non-invasive cancer diagnostics. Several studies reported identification of TP53, PIK3CA, NOTCH1, and CDKN2A mutations in saliva samples obtained from OSCC patients. These findings suggest that saliva may serve as a surrogate source of tumor-derived DNA and provide molecular information comparable to tissue biopsy. **[5,18,20,22]**

Epigenetic biomarkers, particularly DNA methylation signatures, have generated considerable interest because they often represent early events in malignant transformation. Hypermethylation of genes such as p16INK4A, MGMT, DAPK, and RASSF1A has been repeatedly detected in saliva from OSCC patients. Importantly, these alterations may occur during precancerous stages before invasive carcinoma develops. Consequently, epigenetic biomarkers hold significant potential for identifying high-risk individuals and monitoring progression of oral potentially malignant disorders. Their application may ultimately facilitate intervention at stages when treatment outcomes are most favorable. **[18,22–24]**

Recent advances in metabolomics have introduced another promising dimension to saliva-based diagnostics. Cancer cells undergo profound metabolic reprogramming characterized by increased glycolysis, altered amino acid metabolism, enhanced lipid synthesis, and oxidative stress adaptation. These metabolic alterations generate distinct biochemical signatures detectable within saliva. Studies reviewed herein identified increased concentrations of choline, taurine, lactate, phenylalanine, and polyamines among OSCC patients. Such metabolites reflect the altered metabolic requirements of rapidly proliferating tumor cells and provide valuable information regarding disease activity. **[23–25]**

The significance of metabolomic biomarkers lies in their ability to capture functional consequences of genetic and epigenetic alterations. While genomic and transcriptomic biomarkers reveal molecular mechanisms underlying carcinogenesis, metabolites represent the final products of these biological processes. Therefore, metabolomic profiling may provide highly sensitive indicators of disease status. Several studies demonstrated excellent discriminatory capacity for metabolomic signatures, particularly when integrated with proteomic and transcriptomic biomarkers. **[23–25,27]**

One of the most rapidly evolving fields identified during this review is exosome biology. Exosomes are nanosized extracellular vesicles released by both normal and malignant cells and contain a rich cargo of proteins, lipids, mRNAs, microRNAs, and DNA fragments. Because exosomal contents are enclosed within a lipid bilayer membrane, they remain protected from degradation and can circulate stably within biological fluids. Recent studies have demonstrated that salivary exosomes accurately reflect tumor-specific molecular alterations and possess significant diagnostic potential. **[13,14,26–28]**

Particularly noteworthy is the observation that exosomal microRNA panels consistently demonstrated higher diagnostic sensitivity and specificity than many conventional biomarkers. Molecules such as miR-21, miR-31, miR-155, and miR-1246 were frequently enriched within salivary exosomes obtained from OSCC patients. Several studies reported diagnostic accuracies exceeding 90%, suggesting that exosome-based liquid biopsy may represent the next generation of salivary diagnostics. Furthermore, exosomal biomarkers appear capable of distinguishing between early-stage and advanced-stage disease, providing additional prognostic information beyond simple disease detection. **[14,26–29]**

Emerging evidence also suggests that alterations in the oral microbiome may contribute to carcinogenesis and provide novel diagnostic opportunities. Several investigations identified increased abundance of *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella* species, and *Capnocytophaga gingivalis* in OSCC patients. Although microbiome-based diagnostics remain in relatively early stages of development, the findings reviewed here indicate that microbial dysbiosis may complement traditional molecular biomarkers and improve overall diagnostic performance. **[24,27,30]**

Perhaps the most significant trend observed throughout the literature is the transition from single-biomarker strategies toward integrated salivaomics approaches. Individual biomarkers frequently exhibit

variability attributable to age, smoking status, alcohol consumption, oral hygiene, systemic diseases, and methodological differences. Consequently, reliance on a single molecular marker may limit diagnostic reliability. In contrast, multi-omics panels combining proteins, mRNAs, microRNAs, metabolites, exosomal cargo, and microbiome signatures consistently demonstrated superior sensitivity, specificity, and overall diagnostic accuracy. Several recent studies reported area-under-the-curve values approaching 0.95–0.98 for integrated biomarker panels, representing a substantial improvement over individual markers. **[16,24,27–30]**

The emergence of artificial intelligence (AI) and machine learning technologies has further accelerated progress in this field. AI algorithms are capable of analyzing complex multidimensional datasets and identifying patterns that may not be apparent through conventional statistical methods. Several pilot studies reviewed herein demonstrated diagnostic accuracies exceeding 90% when machine learning models were applied to salivaomics datasets. Such approaches may facilitate development of automated, point-of-care diagnostic systems capable of rapidly identifying high-risk individuals within community settings. **[24,27–30]**

Despite these encouraging findings, several challenges remain before routine clinical implementation can be achieved. Significant heterogeneity exists regarding saliva collection methods, sample processing procedures, storage conditions, analytical platforms, and biomarker quantification techniques. Variability introduced by smoking habits, alcohol consumption, medications, periodontal disease, and oral hygiene further complicates interpretation of results. Additionally, many studies included relatively small sample sizes and lacked external validation. These limitations emphasize the need for standardized methodologies and large multicenter prospective studies before salivary biomarkers can be incorporated into routine clinical practice. **[15,16,24,27–30]**

Overall, the findings of the present review clearly demonstrate that salivary biomarkers have evolved from exploratory research tools into highly promising diagnostic candidates with substantial clinical potential. Among the various biomarker categories evaluated, IL-6, IL-8, MMP-9, CYFRA21-1, miR-21, miR-31, exosomal microRNA panels, and integrated multi-omics salivaomics signatures currently possess the strongest evidence base. Continued advances in molecular biology, nanotechnology, biosensor development, liquid biopsy platforms, and artificial intelligence are likely to further enhance diagnostic performance and facilitate clinical translation. Future screening strategies may ultimately utilize saliva-based point-of-care diagnostic devices capable of detecting OSCC at its earliest stages, thereby improving survival rates, reducing treatment-related morbidity, and contributing significantly to global oral cancer control efforts. **[24–30]**

Kumar et al. (2025) evaluated salivary and serum exosomal mRNAs as diagnostic and prognostic biomarkers in patients with OSCC. The investigators reported significantly elevated expression of exosomal **TNF-α, OAZ1, and MMP9 mRNAs** in OSCC patients compared with healthy controls. Salivary exosomal biomarkers demonstrated excellent discriminatory ability and were strongly associated with tumor stage and disease severity. The authors concluded that salivary exosomal mRNAs may serve as reliable, non-invasive biomarkers for both diagnosis and prognosis of oral squamous cell carcinoma. These findings support the growing evidence that exosome-derived molecular signatures possess superior stability and diagnostic accuracy compared with conventional salivary biomarkers [31].

Hu et al. (2025) compared saliva-derived and blood-derived cell-free RNAs for detection of oral squamous cell carcinoma. The study demonstrated that salivary cell-free RNA profiles exhibited strong diagnostic performance and accurately distinguished OSCC patients from healthy individuals. Several RNA signatures identified in saliva showed comparable or even superior sensitivity to blood-based biomarkers. The authors emphasized that saliva represents an easily accessible and highly informative source of tumor-derived nucleic acids and may become an important component of future liquid-biopsy platforms for oral cancer screening and early detection [32].

Hashmi et al. (2026) performed a systematic review evaluating the diagnostic and prognostic potential of salivary microRNAs in oral and head-and-neck squamous cell carcinomas. The review demonstrated that microRNAs such as **miR-21, miR-31, miR-155, and miR-184** consistently showed altered expression in cancer patients and possessed significant diagnostic value. The authors concluded that salivary microRNA panels offer promising sensitivity and specificity for early cancer detection and may facilitate risk stratification, prognosis prediction, and treatment monitoring. However, they emphasized the need for larger multicenter validation studies and standardization of analytical methodologies before routine clinical implementation [33]. Afaq N et al., stated that Early detection significantly improves prognosis, treatment outcomes, and quality of life [34]

CONCLUSION

The present review comprehensively evaluated two decades of research (2005–2026) concerning the role of salivary biomarkers in the early detection of oral squamous cell carcinoma (OSCC). The accumulated evidence clearly demonstrates that saliva is a highly informative biological fluid containing a diverse array of proteins, nucleic acids, metabolites, extracellular vesicles, microbial signatures, and other molecular components that accurately reflect pathological alterations associated with oral carcinogenesis. Unlike conventional tissue biopsy, saliva-based diagnostics offer a non-invasive, painless, economical, and easily repeatable approach for cancer screening and disease monitoring, making them particularly suitable for large-scale population-based screening programs and resource-limited healthcare settings **[7–10,24,27–30]**.

Among the various biomarker categories evaluated, proteomic biomarkers such as IL-6, IL-8, TNF-α, MMP-9, VEGF, CD44, and CYFRA21-1 consistently demonstrated significant diagnostic potential. These molecules reflect inflammatory responses, angiogenesis, extracellular matrix degradation, and tumor progression and have repeatedly shown elevated expression in saliva samples obtained from OSCC patients **[8–12,15,16]**. Similarly, transcriptomic biomarkers including IL8, IL1B, SAT1, OAZ1, DUSP1, and S100P mRNAs have exhibited encouraging sensitivity and specificity for early disease detection and provide valuable insights into active molecular processes occurring within tumor tissues **[10,16–18]**.

The emergence of salivary microRNAs has revolutionized biomarker research owing to their exceptional stability, reproducibility, and strong association with cancer-related pathways. MiR-21, miR-31, miR-184, and miR-155 have emerged as particularly promising diagnostic candidates, whereas reduced expression of tumor-suppressive microRNAs such as miR-125a, miR-145, and members of the miR-200 family has also been associated with malignant transformation **[17,19–22,29]**. Furthermore, advances in genomic and epigenomic profiling have enabled identification of tumor-specific mutations and DNA methylation signatures, providing additional opportunities for detecting early molecular changes preceding overt clinical disease **[18,20,22–24]**.

Recent developments in metabolomics, exosome biology, microbiome research, artificial intelligence, nanotechnology, and salivaomics have further expanded the diagnostic landscape of OSCC. Among these innovations, exosomal biomarkers and integrated multi-omics biomarker panels demonstrated the highest diagnostic performance, frequently achieving sensitivity and specificity values exceeding 90%. The integration of proteomic, transcriptomic, genomic, metabolomic, and exosomal information through machine-learning algorithms appears particularly promising for the development of highly accurate, personalized, and point-of-care diagnostic platforms **[13,14,24–30]**.

Despite substantial progress, several methodological and translational challenges remain before salivary biomarkers can be routinely implemented in clinical practice. Nevertheless, ongoing advances in molecular technologies, standardization protocols, biosensor development, and computational analytics are expected to overcome many of these limitations in the near future. Future multicenter validation studies and prospective clinical trials will be essential to establish standardized diagnostic thresholds and confirm clinical utility across diverse populations **[15,16,24,27–30]**.

Overall, the evidence reviewed strongly supports the potential of salivary biomarkers as valuable tools for early diagnosis, risk assessment, prognosis, treatment monitoring, and recurrence surveillance in oral squamous cell carcinoma. The continued evolution of salivaomics and liquid biopsy technologies is likely to transform oral cancer diagnostics and contribute significantly to earlier detection, improved patient outcomes, reduced healthcare costs, and enhanced global oral cancer control strategies **[24–30]**.

Limitations

Although substantial progress has been achieved in the field of salivary biomarker research for oral squamous cell carcinoma, several important limitations continue to restrict widespread clinical application.

1. Lack of Standardized Saliva Collection Protocols

One of the major limitations identified across studies is the absence of universally accepted protocols for saliva collection, processing, transportation, and storage. Variations in collection methods, collection timing, fasting status, stimulation procedures, and storage conditions may significantly influence biomarker concentrations and affect reproducibility of results **[15,24,27]**.

2. Biological Variability Among Individuals

Salivary composition is influenced by multiple physiological and environmental factors including age, sex, smoking habits, alcohol consumption, dietary patterns, oral hygiene status, periodontal disease, medications, circadian rhythm, and systemic illnesses. These variables may introduce substantial interindividual variability and complicate interpretation of biomarker data **[11,15,24,29]**.

Limited Sample Sizes

Many published investigations involved relatively small patient cohorts and single-center study designs. Limited sample sizes reduce statistical power and may compromise generalizability of findings across different ethnic, geographic, and socioeconomic populations **[16,21,27,30]**.

4. Lack of Large Multicenter Validation Studies

Although numerous biomarkers have demonstrated promising diagnostic performance, only a limited number have undergone rigorous multicenter validation. Consequently, reproducibility across independent populations remains insufficiently established for many candidate biomarkers **[15,16,27–30]**.

5. Heterogeneity of Analytical Techniques

Different studies employed diverse analytical platforms such as ELISA, quantitative PCR, digital PCR, microarray analysis, next-generation sequencing, mass spectrometry, and biosensor-based technologies. This methodological heterogeneity makes direct comparison between studies challenging and contributes to variability in reported diagnostic performance **[16,24,25,27]**.

6. Absence of Uniform Diagnostic Cut-Off Values

Many biomarkers currently lack standardized threshold values for clinical diagnosis. Differences in assay sensitivity, laboratory methodology, and patient populations contribute to inconsistencies in defining optimal diagnostic cut-off points **[15,24,29,30]**.

7. Influence of Oral Inflammatory Conditions

Periodontitis, gingivitis, oral infections, traumatic lesions, and other inflammatory oral diseases may alter concentrations of cytokines and inflammatory mediators such as IL-6, IL-8, and TNF-α, potentially reducing specificity for OSCC detection **[11,15,16]**.

8. Limited Longitudinal Studies

Most available investigations are cross-sectional or case-control studies. Relatively few longitudinal studies have evaluated biomarker dynamics during disease progression, treatment response, recurrence, or long-term follow-up, limiting understanding of prognostic utility **[16,18,27]**.

9. High Cost of Advanced Omics Technologies

Although next-generation sequencing, proteomics, metabolomics, exosome analysis, and artificial intelligence-based approaches have shown exceptional promise, these technologies often require sophisticated instrumentation, specialized expertise, and substantial financial investment, limiting accessibility in many healthcare systems **[24,25,27–30]**.

10. Regulatory and Clinical Implementation Challenges

Before salivary biomarker assays can be incorporated into routine clinical practice, robust evidence regarding analytical validity, clinical validity, cost-effectiveness, and regulatory approval is required. At present, most candidate biomarkers remain within the research domain and have not yet achieved widespread clinical adoption **[27–30]**.

Declarations:

Conflicts of interest: There is no any conflict of interest associated with this study

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