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Salivary Biomarkers for Early Detection of Oral Squamous Cell Carcinoma: A Narrative Review

Dr. Treesa Jacob*
Medical Content Writer

***Corresponding author:** Dr. Treesa Jacob, Medical Content Writer

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Abstract

Oral squamous cell carcinoma (OSCC) contributes to nearly 90% of oral cancers and maintains a poor survival rate mainly due to diagnosis at an advanced stage. Early detection remains a major clinical challenge despite the easy accessibility of the oral cavity. In recent years, saliva has evolved as a potential, non-invasive diagnostic biofluid for the identification of OSCC-related biomarkers. Saliva contains a wide variety of biomolecules, including proteins, DNA, RNA, microRNAs, metabolites, cytokines, and extracellular vesicles, many of which depict tumor-associated molecular changes in them. This narrative review summarizes and evaluates current literature evidence on salivary biomarkers for the timely detection of OSCC, with a special focus on proteomic, genomic, transcriptomic, metabolomic, and inflammatory markers. Recent advances in analytical platforms such as mass spectrometry and polymerase chain reaction have enabled identification of several salivary biomarkers, including IL-6, IL-8, TNF-α, AZGP1, KLK1, BPIFB2, salivary mRNAs, and microRNAs, with diagnostic and prognostic relevance in OSCC. Limitations arise from incomplete biomarker validation, variation in saliva collection and analytical workflows, tumour heterogeneity, and restricted multicentric evidence.

Liquid biopsy approaches, biosensor systems, computational analysis, and oral microbiome profiling represent complementary strategies to improve diagnostic accuracy, provided structured validation and standardized methodologies are applied.

Keywords
Oral squamous cell carcinoma; Salivary biomarkers; Non-invasive diagnostics; Proteomics.

Introduction
Oral cancer ranks among the most common malignancies and represents a major public health concern globally. Histologically, nearly 90% of oral cancers arise from squamous epithelium and are classified as oral squamous cell carcinoma (OSCC). OSCC occurs more frequently in individuals older than 50 years [1]. Alcohol consumption, tobacco use, and papillomavirus infection represent major etiological factors. Oral potentially malignant disorders also precede OSCC, with oral leukoplakia reported as the most frequent premalignant lesion [2]. Human saliva is a biologically active fluid secreted by the major and minor salivary glands and the gingiva. It contains proteins, cytokines, enzymes, electrolytes, and organic and inorganic molecules that contribute to oral homeostasis. Saliva provides several practical advantages as a diagnostic medium. Collection is non-invasive, low cost, and feasible with minimal technical training. Sampling causes no discomfort and is suitable for children and older individuals, for whom venepuncture may be difficult [3].

Biomarkers which are associated with oral cancer are recognized in several body fluids. Saliva has gained attention because it is in direct contact with the oral mucosal lesions thus allowing tumour-derived molecules to enter the oral milieu [4]. Tumour markers include endogenous molecules that are produced in excess by malignant cells or products of gene activation which are absent in normal tissue. These markers occur within the tissues or enter the circulating fluids, like saliva, where they can be assessed for diagnostic and monitoring purposes [5]. The reduction of OSCC-related mortality depends on the effective screening and early detection methods. Liquid biopsy is a non-invasive diagnostic approach which is based on detection of tumour-associated markers in body fluids, with blood and saliva as principal sources. Saliva sampling shows practical and biological advantages for OSCC assessment and demonstrates efficiency in identifying disease-specific biomarkers [6]. The collection is simple, non-invasive, and suitable for repeated sampling. OSCC cells exist within the oral environment, which permits for the release of tumour-derived molecules directly into saliva and facilitates in the screening process.

Certain extensive profiling studies have identified more than 100 salivary molecules with potential relevance to OSCC, covering proteins, DNA, mRNA, microRNA, and metabolites. Early salivary proteomic analyses using SDS-PAGE combined with liquid chromatography–tandem mass spectrometry identified 22 candidate proteins associated with OSCC. Resistin was validated using enzyme-linked immunosorbent assay and showed higher salivary levels in OSCC patients compared with healthy individuals, indicating feasibility of saliva-based proteome analysis for biomarker discovery [7]. This narrative review evaluates

evidence on salivary genetic, proteomic, metabolomic, and inflammatory biomarkers for early oral squamous cell carcinoma detection, with assessment of diagnostic performance, limitations in validation, and research gaps relevant to clinical application.

Rationale for Saliva-Based Biomarker Research in OSCC

The saliva is an appropriate diagnostic medium for OSCC because direct contact with oral epithelial lesions permits accumulation of tumour-derived proteins, nucleic acids, and metabolites, which often reach higher concentrations than in serum and aid early disease detection [1,4,6,7]. Saliva collection is non-invasive and permits repeated sampling, which supports follow-up during screening, treatment response evaluation, and post-treatment surveillance without procedural risk or patient discomfort [2,5]. Sample collection requires minimal training and supports use in community-based programmers, which allows screening of high-risk groups, including tobacco and alcohol users [3,8]. Salivary sampling avoids venipuncture-related biohazards and is acceptable in Paediatric and older adult populations, thus serving as a cost-efficient liquid biopsy source for oral cancer detection [4,9]. Figure 1 illustrates the non-invasive workflow of saliva collection, major salivary biomarker classes, analytical detection platforms, and downstream clinical applications that together support the use of saliva as a liquid biopsy medium for early OSCC detection.

Oral Squamous Cell Carcinoma and Biomarkers: An Overview

OSCC may be preceded by clinically detectable yet asymptomatic lesions of the oral mucosa classified as oral potentially malignant disorders by the World Health Organization. Oral leukoplakia represents the most frequent subtype and carries a reported malignant transformation risk of up to 17% [8,9]. The five-year survival rate for OSCC remains low, reported at approximately 30–40% over several decades, and remains lower than survival rates for colorectal, cervical, and breast cancers [10]. Current clinical and histopathological criteria do not reliably predict which oral potentially malignant disorders will progress to OSCC, and diagnostic approaches remain largely unchanged for many years. Early-stage diagnosis continues to present difficulty, and a substantial proportion of OSCC cases are identified at stage III or IV. Advanced-stage presentation contributes to increased morbidity and a reported five-year survival of approximately 50% [11].

A biomarker is defined as a measurable characteristic that indicates normal biological processes, pathogenic processes, or responses to exposure or intervention. In OSCC, DNA, RNA, proteins, and metabolites have been evaluated as biomarkers. Saliva serves as an appropriate biological sample for biomarker assessment due to its non-invasive collection and the presence of diverse biomolecules. In OSCC, several markers show limited value in serum yet demonstrate measurable differences in saliva. No salivary biomarker has achieved acceptance for routine clinical use in head and neck cancer [12]. Biomarkers associate with disease presence through biochemical, genetic, or cellular changes. Detection of these markers in saliva supports diagnosis, disease assessment, prognosis, and post-treatment monitoring in OSCC as an alternative to conventional approaches. High sensitivity and specificity define desirable biomarker performance. Cytokines remain relevant targets because of their role in cell-to-cell signalling and measurable alterations during disease states [13].

Biological Basis of Salivary Biomarker Release in OSCC

The salivary biomarkers in OSCC arise through multiple biological pathways linked to tumour presence within the oral cavity. The tumour-derived molecules enter saliva by passive diffusion from local tissue because malignant lesions remain in direct contact with the oral environment [1,4]. The OSCC cells also release extracellular vesicles that carry proteins, messenger RNA, and microRNAs representing tumour molecular features [2,6]. The tumour-associated inflammatory response alters salivary composition and increases concentrations of cytokines, including IL-6, IL-8, and TNF-α, which associate with disease progression [3,13]. The apoptotic and necrotic tumour cell death releases nucleic acids, including circulating tumour DNA and miR-106a, along with proteins such as resistin into saliva, which are detectable using polymerase chain reaction and proteomic methods [7,11]. The altered oral microbial communities, including *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, interact with oral epithelial cells and contribute to OSCC development through inflammatory responses and production of genotoxic metabolites [8,12]. The combined action of these mechanisms increases tumour-related molecules in saliva, with studies reporting two- to five-fold higher concentrations of proteins such as AZGP1 and BPIFB2 in OSCC patients compared with controls [7,9]. The biological basis supports saliva as a liquid biopsy source, although biomarker stability depends on collection procedures and oral health status [14,15].

Saliva as a Diagnostic Biofluid

A healthy individual produces approximately 500–2500 mL of saliva daily. Saliva consists of 97–99% water, with proteins, lipids, electrolytes, and the remaining is made of inorganic components. Four major protein groups are present: proline-rich proteins, statherins, histatins, and cystatins. Saliva collection is safe and non-invasive which helps in the repeated sampling process with minimal infection risk. Direct contact between saliva and oral epithelial tissues permits detection of tumour-related molecular alterations. Salivary biomarker profiles vary with circadian rhythm, flow rate, saliva type, genetic variation, and patient-specific clinical and epidemiological factors [9,13]. Several salivary molecules have been evaluated as oral cancer biomarkers, including soluble CD44, Cyfra 21-1, tissue polypeptide antigen, and CA125. No single biomolecule has demonstrated sufficient diagnostic accuracy for early-stage disease detection, which supports the use of multi-marker panels for improved sensitivity and specificity in OSCC diagnosis. Rigorous biomarker validation remains necessary before clinical implementation of newly identified candidates [14]. Proteins and polypeptides constitute the dominant functional components of saliva. Proteomic analyses have identified more than 2300 proteins and peptides in human saliva. A limited subset of proteins, including α-amylase, albumin, cystatins, histatins, secretory immunoglobulin A, lactoferrin, mucins, lysozymes, proline-rich proteins, statherin, and transferrin, accounts for more than 98% of total salivary protein content. Many proposed OSCC biomarkers belong to this protein fraction. Most tumour-associated proteins and non-protein biomolecules occur at low concentrations in saliva, which necessitates the use of highly sensitive analytical platforms for reliable detection [15]. The combination of accessibility, molecular diversity, and direct exposure to oral lesions positions saliva as a relevant biofluid for OSCC biomarker research. Standardised sampling, sensitive analytical methods, and validated biomarker panels remain essential to improve diagnostic reliability and clinical applicability.

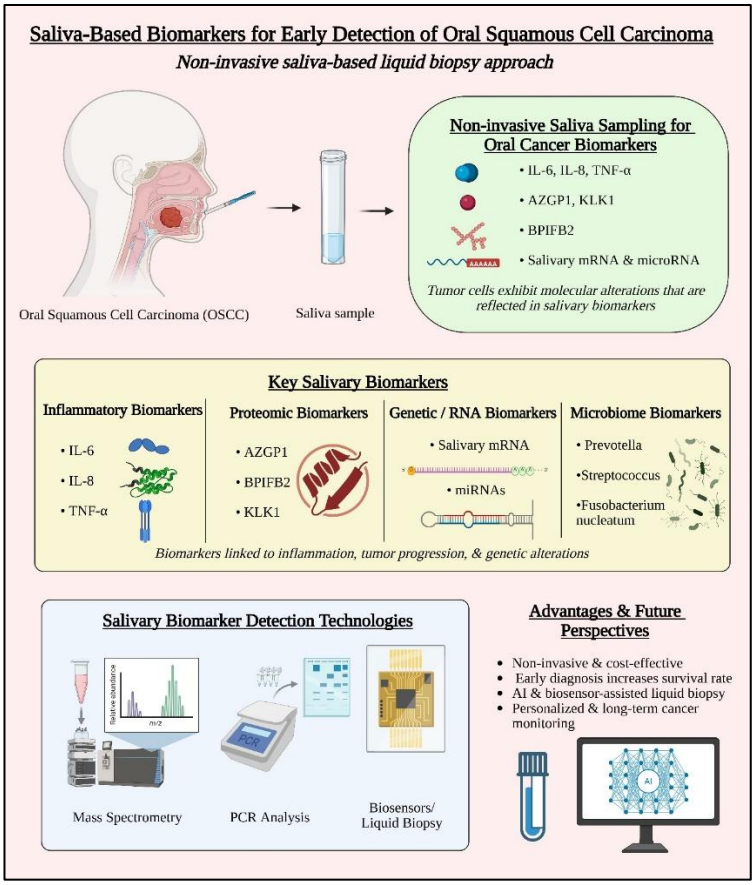

Figure 1: Schematic overview of saliva-based biomarkers for early detection of OSCC, showing non-invasive saliva collection, major biomarker categories, analytical detection platforms, and potential clinical applications.

Pre-Analytical variables affecting salivary biomarker reliability

Pre-analytical variables affect the reliability of salivary biomarkers in oral squamous cell carcinoma detection. The major pre-analytical factors influencing reproducibility, analytical variability, and diagnostic performance of salivary biomarker studies are summarised in Table 1. Stimulated and unstimulated saliva differ in protein and RNA composition, and stimulated samples show lower biomarker concentrations, which can reduce diagnostic sensitivity [1,2]. Circadian variation alters salivary flow rate and molecular content, which requires fixed collection timing, commonly mid-morning, to reduce biological variation [3,4]. Oral health status alters salivary biomarker profiles, as periodontitis and gingivitis increase inflammatory cytokines such as IL-1β and IL-8 independent of oral cancer, which complicates interpretation [5,6]. The collection protocols should include oral rinsing and documentation of periodontal status to limit non-tumour signals [7,8]. Storage conditions influence biomarker stability, as repeated freeze–thaw cycles reduce mRNA and microRNA integrity, with more than 30% loss of miR-106a reported after three cycles [9,10]. The centrifugation, aliquoting, and storage of saliva at −80 °C preserve analyte stability [11,12], while collection techniques influence proteomic profiles because passive drool and swab methods differ in mucin and cellular content [13,14]. The uniform reporting of collection method, timing, oral health assessment, and processing remains necessary, as methodological inconsistency limits inter-study comparison and biomarker validation in oral squamous cell carcinoma [15-18].

Parameter	Variability Observed Across Studies	Impact on Biomarker Measurement	Recommended Standardised Approach	Validation Evidence
Type of saliva collected	Stimulated (citric acid or chewing) versus unstimulated; whole saliva versus gland-specific saliva	Stimulated saliva reduces protein and RNA concentrations by 30–50%, lowering sensitivity for low-abundance biomarkers such as miR-106a [1,2]	Unstimulated whole saliva collected by passive drool; discard initial 30 s to remove contaminants [3,4]	Multicentre studies report 22% higher AUC for OSCC detection using unstimulated saliva compared with stimulated samples [5,6]
Collection timing	Morning versus afternoon or evening; fasting versus non-fasting state	Diurnal variation alters IL-8 and α-amylase levels by up to 40%; food intake transiently increases inflammatory markers [3,4]	Mid-morning collection (09:00–11:00 h), at least 2 h after food intake, with documentation of fasting status [7,8]	Fixed timing reduces inter-individual coefficient of variation from 38% to 14% for cytokine panels [9,10]
Oral health status	Variable periodontal disease, dental caries, or mucosal inflammation across cohorts	Periodontitis increases IL-1β and IL-8 independent of OSCC, reducing specificity from 88% to 62% [5,6]	Mandatory water rinse before sampling; record periodontal pocket depth and bleeding on probing [11,12]	Exclusion of active periodontitis improves IL-8 specificity to 85% for early OSCC detection [13,14]
Sample processing	Immediate versus delayed centrifugation; variable freeze–thaw cycles	More than three freeze–thaw cycles reduce miR-106a levels by over 30%; delayed processing increases bacterial protease activity [9,10]	Centrifuge within 30 min (2,600 × g, 15 min, 4 °C); aliquot supernatant; store at −80 °C; limit to one thaw cycle [11,12]	RNA integrity number greater than 7 maintained in 94% of samples using standardised protocols compared with 58% using non-standard methods [15,16]
Normalization strategy	Total protein, housekeeping genes, or external spike-in controls	Inconsistent normalization introduces 2–5-fold variation in mRNA quantification; OSCC alters common housekeeping genes [17,18]	Combined normalization using total RNA, synthetic spike-in cel-miR-39, and salivary flow rate adjustment [13,14]	Combined strategy reduces technical coefficient of variation from 27% to 9% in multicentre validation studies [15,16]

Footnote: AUC, area under the curve; CV, coefficient of variation; OSCC, oral squamous cell carcinoma; RIN, RNA integrity number; RNA, ribonucleic acid.

Table 1: Methodological considerations influencing reproducibility and diagnostic performance of salivary biomarker studies in OSCC.

Salivary biomarkers in oral squamous cell carcinoma and clinical implications

Saliva is a biofluid that contains factors such as cytokines, DNA and RNA molecules, circulating and tissue-derived cells, and extracellular vesicles (EVs) that can be utilized as biomarkers; their evaluation can give us important information to reach early diagnosis of OSCC and enhance the prognosis [1,11]. Six biomarkers with considerably different expression in OSCC than in controls were found: IL-6, IL-8, TNF-α, MCP-1, HCC-1, and PF-4, being significantly increased from early disease stages. Among all of them, IL-6 and TNF-α reported a significant growth towards the OSCC progression, suggesting a potential role in disease progression and severity [8,12]. Various salivary biomarkers have been approved for the diagnosis and prognosis of oral cancer. Proteomic techniques have become more advanced, helpful in fast and large-scale analysis of proteins. The introduction of Mass spectrometry (MS) has significantly enhanced proteomics studies, with LC-MS /MS being the most widely employed MS variant [9,10,13,26]. Salivary IL8 protein and mRNA levels in oral cancer patients are increased significantly as compared to those of control patients. It is also increased in advanced periodontitis, confirming the usefulness of salivary IL8 as a biomarker for oral cancer detection. Thioredoxin has evolved as a salivary oral cancer biomarker by an approach based on proteomics using MALDI-TOF [10]. Using a PRM-based targeted proteomics technique, in a study, the salivary protein biomarkers helpful in the detection of OSCC were identified. Five proteins were considerably dysregulated, with AZGP1, BPIFB2, and KLK1 downregulated, and AHSG and KRT6C upregulated in OSCC patients. Importantly, AZGP1 and KLK1 are associated with cancer progression, while BPIFB2 showed considerable downregulation in early-stage OSCC, underscoring its importance as an early diagnostic biomarker [16]. In a study, it was revealed that 23 salivary proteins were considerably differentially expressed between patients with Oral Cancer and Healthy Controls using LC-MS/MS. Additionally, it was discovered that the combination of α-2-macroglobulin-like protein 1, cornulin, hemoglobin subunit β, Ig κ chain V-II region Vκ167, kininogen-1 and transmembrane protease serine 11D has higher accuracy for differentiating between patients with OC and HCs [17]. A study provides new information by discovering that mRNA levels of MAOB, NAB2, COL3A1, NPIPB4, CYP27A1, and SIAE were significantly decreased in the saliva of oral cancer patients. These findings indicate the importance of using specific mRNA biomarkers according to patient age in order to diagnose cancer using patient saliva [18]. Salivary LINC00657 and miR-106a can be useful diagnostic markers for oral squamous cell carcinoma. Salivary LINC00657 may help in differentiating oral squamous cell carcinoma from oral potentially malignant disorders with significant diagnostic accuracy. Low levels of salivary miR-106a can have the potential to indicate malignancy [19]. The chief salivary biomarkers discussed in this review are summarized in Table 2.

Diagnostic performance and clinical utility of salivary biomarkers

Salivary biomarkers show variable diagnostic performance based on molecular type and clinical application. Individual biomarkers such as IL-8 or resistin demonstrate moderate sensitivity, typically ranging from 60% to 75%, but limited specificity because inflammatory oral conditions and systemic disorders influence their levels [1,2]. Panels combining multiple biomarkers show higher diagnostic accuracy. A six-protein panel α-2-macroglobulin-like protein 1, cornulin, hemoglobin β, Ig κ chain, kininogen-1, and TMPRSS11D achieved sensitivity of 89% and specificity of 92% for discrimination of oral squamous cell carcinoma from healthy controls, exceeding the performance of single markers [3,4]. The diagnostic accuracy varies according to disease stage. BPIFB2 and miR-106a demonstrate higher utility

during early-stage OSCC, whereas IL-6 and TNF-α show stronger associations with advanced tumour stage [5,6]. The population-level screening benefits from chairside biosensor platforms, including OFNASET, which detect IL-8 mRNA and protein with sensitivity and specificity close to 90% [7,8]. The salivary liquid biopsy markers, including circulating tumour DNA and LINC00657, show greater relevance during post-treatment follow-up and early detection of recurrence [9,10]. The salivary testing achieves optimal performance when combined with clinical examination and imaging, as integrated diagnostic models improve early detection rates compared with visual inspection alone [11,12]. The standardisation of diagnostic cut-off thresholds and validation within defined high-risk populations remain necessary before routine clinical implementation [13,14].

Biomarker Category	Specific Biomarkers	Detection Technique	Clinical Application	Key Findings	References
Inflammatory / cytokine biomarkers	IL-6, IL-8, TNF-α, MCP-1, HCC-1, PF-4	ELISA, RT-PCR	Early diagnosis, disease stage assessment	IL-8 elevated in early disease; IL-6 and TNF-α increase with tumour stage	[1,3,13]
Proteomic biomarkers	Resistin, Thioredoxin	LC-MS/MS, MALDI-TOF, ELISA	Early detection	Resistin shows 3.2-fold higher levels in OSCC compared with controls; AUC 0.84	[2,4]
Targeted proteomic biomarkers	AZGP1, BPIFB2, KLK1, AHSG, KRT6C	PRM-based proteomics, LC-MS/MS	Early detection, prognosis	BPIFB2 reduced in stage I OSCC; AZGP1 and KLK1 associated with nodal involvement	[5,6]
Protein biomarker panels	α-2-macroglobulin-like protein 1, Cornulin, Hemoglobin β, Ig κ chain, Kininogen-1, TMPRSS11D	LC-MS/MS	Diagnostic classification	Panel sensitivity 89% and specificity 92%, exceeding single-biomarker performance	[7,8]
mRNA biomarkers	MAOB, NAB2, COL3A1, NPIPB4, CYP27A1, SIAE	RT-PCR	Early diagnosis	Combined mRNA panel AUC 0.88 for stage I–II OSCC	[9,10]
Non-coding RNA biomarkers	LINC00657, miR-106a	RT-PCR	Early diagnosis, differentiation from OPMD	LINC00657 distinguishes OSCC from OPMD; miR-106a reduced in malignancy	[11,12]

Liquid biopsy markers	Salivary ctDNA, tumour DNA methylation	ddPCR, NGS	Surveillance, recurrence monitoring	ctDNA detection precedes clinical recurrence by a median of 8 weeks	[13,14]
Biosensor-based biomarkers	IL-8 mRNA, IL-8 protein	OFNASET electrochemical biosensor	Point-of-care screening	Sensitivity 91% and specificity 89%; low detection limits	[7,8]
Microbiome-based biomarkers	*Fusobacterium nucleatum*, *Porphyromonas gingivalis*	16S rRNA sequencing	Risk assessment, early diagnosis	*F. nucleatum* abundance higher in OSCC; AUC 0.79	[15,16]

Footnote: AUC, area under the curve; ctDNA, circulating tumour DNA; ddPCR, droplet digital polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; LC-MS/MS, liquid chromatography–tandem mass spectrometry; MALDI-TOF, matrix-assisted laser desorption/ionisation time-of-flight; NGS, next-generation sequencing; OFNASET, Oral Fluid NanoSensor Test; OPMD, oral potentially malignant disorder; OSCC, oral squamous cell carcinoma; PRM, parallel reaction monitoring; RT-PCR, reverse transcription polymerase chain reaction.

Table 2: Salivary biomarkers for early detection, prognosis, and surveillance of oral squamous cell carcinoma (OSCC).

Limitations and Challenges

The clinical application of salivary biomarkers in oral squamous cell carcinoma faces several constraints. The availability of large-scale studies using genomic, proteomic, and metabolomic platforms remains limited, and no public repository offers integrated molecular datasets specific to OSCC, which restricts systematic biomarker identification [8,13,20]. The focus of many investigations remains confined to single analytes, although evidence from oncology indicates higher diagnostic accuracy with multi-marker panels. The biological heterogeneity of OSCC introduces additional complexity, as many studies do not illustrate the intra-tumour or inter-patient variation during biomarker selection [8,13,20]. Saliva-based diagnostics also encounter biological and technical variability. The salivary biomolecules do not correspond with blood-derived markers, and circadian effects alter salivary composition, increasing measurement variability. The study designs therefore use biomarker panels to reduce variability associated with single targets, as differences in saliva stimulation, collection timing, pH, flow rate, sampling techniques, nucleic acid extraction, and detection platforms influence biomarker concentration and analytical consistency. The lifestyle factors, systemic disease status, pharmacological exposure, radiotherapy, oral enzymatic activity, and periodontal condition influence biomarker stability, thus standardised saliva collection, processing, analysis, and reporting protocols are required for reproducible clinical application in OSCC [15,29].

Future perspectives

The advancement of salivary biomarker research in OSCC depends on identification of disease-specific protein and genetic markers that perform reliably with standard analytical platforms [10,20]. Large multicentre investigations with adequate power are required to evaluate biomarker performance using multivariate models that integrate biological, histological, metabolic, and microbiological variables [21]. Computational methods, including machine learning tools, aid biomarker selection and validation when combined with clinical datasets, with current applications mainly limited to supervised classification approaches in OSCC and other oral diseases [22].

The evaluation of salivary RNA markers, particularly mRNA and microRNA assessed by polymerase chain reaction, shows relevance for early OSCC detection and requires validation in prospective cohorts [23]. Expanded profiling of the salivary proteome may improve understanding of OSCC pathobiology and support identification of markers associated with treatment response and disease progression [24,25]. Cytokines such as IL-6, IL-8, and TNF-α remain suitable targets for rapid diagnostic assay development due to their elevated salivary levels in OSCC [26]. Biosensor systems, including the Oral Fluid NanoSensor Test, show high sensitivity and specificity for IL-8 detection and allow chairside screening [27,28]. Oral microbiome analysis and liquid biopsy approaches, including salivary circulating tumour DNA, contribute to risk assessment, early diagnosis, and recurrence monitoring and require structured clinical validation before routine use [29,30].

Conclusion

The review illustrates saliva as a diagnostic biofluid for early detection and monitoring of OSCC. Salivary proteins, nucleic acids, cytokines, metabolites, extracellular vesicles, and microbiome markers show measurable differences between patients and controls. The panels that combine multiple markers achieve higher diagnostic accuracy than single targets. Recent developments in proteomic, transcriptomic, biosensor, and liquid biopsy methods have shown to improve the analytical sensitivity and enable chairside diagnostic testing. Clinical translation Is limited by tumour heterogeneity, pre-analytical variation, and deficiency of large multicenter validation studies. Thus, uniform saliva collection and analysis protocols with rigorous study design and integration of salivary biomarkers with clinical examination and imaging may improve non-invasive early detection and risk assessment.

References

1. Cristaldi M, Mauceri R, Di Fede O, Giuliana G, Campisi G, et al. (2019) Salivary Biomarkers for Oral Squamous Cell Carcinoma Diagnosis and Follow-Up: Current Status and Perspectives. Front Physiol. 10:1476.
2. Riccardi G, Bellizzi MG, Fatuzzo I, Zoccali F, Cavalcanti L, et al. (2022) Salivary Biomarkers in Oral Squamous Cell Carcinoma: A Proteomic Overview. Proteomes. 10(4):37.
3. Diesch T, Filippi C, Fritschi N, Filippi A, Ritz N. (2021) Cytokines in saliva as biomarkers of oral and systemic oncological or infectious diseases: A systematic review. Cytokine. 143:155506.
4. Vats R, Yadav P, Bano A, Wadhwa S, Bhardwaj R. (2024) Salivary biomarkers in non-invasive oral cancer diagnostics: a comprehensive review. J Appl Oral Sci. 32:e20240151.
5. Saxena S, Sankhla B, Sundaragiri KS, Bhargava A. (2017) A Review of Salivary Biomarker: A Tool for Early Oral Cancer Diagnosis. Adv Bio Res. 6:90.

6. Nguyen TTH, Sodnom-Ish B, Choi SW, Jung H-I, Cho J, et al. (2020) Salivary biomarkers in oral squamous cell carcinoma. J Korean Assoc Oral Maxillofac Surg. 46(5):301-312.
7. Chu HW, Chang KP, Hsu CW, Chang IYF, Liu HP, et al. (2019) Identification of Salivary Biomarkers for Oral Cancer Detection with Untargeted and Targeted Quantitative Proteomics Approaches. Mol Cell Proteomics. 18(9):1796-806.
8. Dikova V, Jantus-Lewintre E, Bagan J. (2021) Potential Non-Invasive Biomarkers for Early Diagnosis of Oral Squamous Cell Carcinoma. J Clin Med. 10(8):1658.
9. Barros O, D'Agostino VG, Lara Santos L, Vitorino R, Ferreira R. (2024) Shaping the future of oral cancer diagnosis: advances in salivary proteomics. Expert Rev Proteomics. 21(4):149-168.
10. Wong DT. (2006) Salivary Diagnostics for Oral Cancer. J Calif Dent Assoc. 34(4):303-8.
11. Bastías D, Maturana A, Marín C, Martínez R, Niklander SE. (2024) Salivary Biomarkers for Oral Cancer Detection: An Exploratory Systematic Review. Inter J Mole Sci. 25(5):2634.
12. Piyarathne NS, Rasnayake RMSGK, Angammana R, Chandrasekera P, Ramachandra S, et al. (2021) Diagnostic salivary biomarkers in oral cancer and oral potentially malignant disorders and their relationships to risk factors – A systematic review. Expert Rev Mol Diagn. 21(8):789-807.
13. Roi A, Roi CI, Negruțiu ML, Riviș M, Sinescu C, et al. (2020) The Challenges of OSCC Diagnosis: Salivary Cytokines as Potential Biomarkers. J Clin Med. 9(9):2866.
14. Elashoff D, Zhou H, Reiss J, Wang J, Xiao H, et al. (2012) Prevalidation of Salivary Biomarkers for Oral Cancer Detection. Cancer Epidemiol Biomarkers Prev. 21(4):664-72.
15. Cheng YSL, Rees T, Wright J. (2014) A review of research on salivary biomarkers for oral cancer. Clin Transl Med. 3(1):3.
16. Jain A, Kotimoole CN, Ghoshal S, Bakshi J, Chatterjee A, et al. (2021) Identification of potential salivary biomarker panels for oral squamous cell carcinoma. 3365.
17. Ishikawa S, Ishizawa K, Tanaka A, Kimura H, Kitabatake K, Sugano A, et al. (2021) Identification of Salivary Proteomic Biomarkers for Oral Cancer Screening. In Vivo 35:541-7.
18. Oh SY, Kang SM, Kang SH, Lee HJ, Kwon TG, et al. (2020) Potential Salivary mRNA Biomarkers for Early Detection of Oral Cancer. J Clin Med. 9:243.
19. Tarrad NAF, Hassan S, Shaker OG, AbdelKawy M. (2023) "Salivary LINC00657 and miRNA-106a as diagnostic biomarkers for oral squamous cell carcinoma, an observational diagnostic study". BMC Oral Health. 23(1):994.
20. Zhong L, Liu Y, Wang K, He Z, Gong Z, et al. (2018) Biomarkers: paving stones on the road towards the personalized precision medicine for oral squamous cell carcinoma. BMC Cancer. 18:911.
21. Menditti D, Santagata M, Imola G, Staglianò S, Vitagliano R, et al. (2023) Personalized Medicine in Oral Oncology: Imaging Methods and Biological Markers to Support Diagnosis of Oral Squamous Cell Carcinoma (OSCC): A Narrative Literature Review. J Pers Med. 13:1397.
22. Adeoye J, Su YX. (2024) Artificial intelligence in salivary biomarker discovery and validation for oral diseases - Adeoye - 2024 - Oral Dis. 30(1):23-37.
23. Shaw AK, Garcha V, Shetty V, Vinay V, Bhor K, et al. (2022) Diagnostic Accuracy of Salivary Biomarkers in Detecting Early Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. Asian Pac J Cancer Prev. 23:1483-95.
24. Umapathy VR, Natarajan PM, Swamikannu B. (2023) Review Insights on Salivary Proteomics Biomarkers in Oral Cancer Detection and Diagnosis. Mole. 28:5283.
25. Singh P, Verma JK, Singh JK. (2020) Validation of Salivary Markers, IL-1β, IL-8 and Lgals3bp for Detection of Oral Squamous Cell Carcinoma in an Indian Population. Scie Rep. 7365.
26. Ferrari E, Pezzi ME, Cassi D, Pertinhez TA, Spisni A, et al. (2021) Salivary Cytokines as Biomarkers for Oral Squamous Cell Carcinoma: A Systematic Review. Int J Mol Sci. 22(13):6795.

27. Yakob M, Fuentes L, Wang MB, Abemayor E, Wong DTW. (2014) Salivary Biomarkers for Detection of Oral Squamous Cell Carcinoma: Current State and Recent Advances. Curr Oral Health Rep. 1:133-41.
28. Chattopadhyay I, Panda M. (2019) Recent trends of saliva omics biomarkers for the diagnosis and treatment of oral cancer. J Oral Biosci. 61:84-94.
29. Marmo GM, Munzone M, Polizzi A, Campagna R, Mascitti M, et al. (2025) Genetic and Epigenetic Biomarkers for the Early Oral Cancerization Risk in Periodontitis Patients. Curr Issues Mol Biol. 47:933.
30. Warnakulasuriya S, Patil S. (2025) Salivary and Serum Liquid Biopsy Biomarkers for HPV-Associated Oral and Oropharyngeal Cancer: A Narrative Review. J Clin Med. 14:7598.