



Salivary Biomarkers for the Early Detection and Prognostic Stratification of Oral Squamous Cell Carcinoma

Hafiz Waqas Ahmed¹, Munazza Kafait², Ayesha Rais³, Zakia Yaqoob³, Bilal Basit⁴, Javeria Saleem⁵

¹Department of Oral and Maxillofacial Surgery, Mayo Hospital/ King Edward Medical University, Lahore, ²Department of Oral & Maxillofacial Surgery, Lahore Specialists Clinic, Lahore, ³Department of Oral & Maxillofacial Surgery, Sandeman Provincial Hospital, Bolan University of Medical and Health Sciences, Quetta, ⁴Department of Oral & Maxillofacial Surgery, Rashid Latif Dental College, Lahore, ⁵Department of Public Health, Green international University, Lahore, Pakistan.

ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) remains a major public health burden, especially in low- and middle-income countries. Traditional diagnostic modalities are often invasive and fail to detect early-stage disease. Saliva, as a non-invasive and readily accessible diagnostic fluid, has gained increasing attention for its potential to reflect molecular changes associated with malignancy. This study explored the diagnostic and prognostic utility of salivary biomarkers spanning genomic, transcriptomic, proteomic, exosomal, and metabolomic classes in patients with OSCC. To assess the diagnostic accuracy and predictive value of selected salivary biomarkers for OSCC using logistic regression analysis and stage-wise correlation.

Methods: This multicenter case-control study from January 2015 to March 2025 enrolled 400 participants: 200 confirmed OSCC cases, 120 patients with oral potentially malignant disorders (OPMDs), and 80 healthy controls. Unstimulated saliva samples were collected and analyzed using qPCR, ELISA, and mass spectrometry for key biomarkers including EGFR, p53, IL-8, Ki-67, miR-423-5p, miR-1246, CYFRA 21-1, SAT1,

NUS1, sialic acid, and exosomal EGFR. SPSS v.26 was used for data analysis. Logistic regression analysis was used to evaluate associations between biomarker levels and OSCC risk, while ROC curves assessed diagnostic accuracy (AUC). P value of <0.05 was considered significant.

Results: Logistic regression revealed strong associations between elevated salivary levels of exosomal miR-1246 (OR=2.90, 95% CI: 2.10–3.75), IL-8 (OR=2.10, 95% CI: 1.55–2.80), EGFR (OR=2.45, 95% CI: 1.80–3.34), and miR-423-5p (OR=2.70, 95% CI: 1.95–3.50) with OSCC presence ($p < 0.001$). Exosomal markers demonstrated >90% diagnostic accuracy (AUC > 0.90), outperforming genomic and proteomic markers. Stage-wise analysis showed increasing expression trends for IL-8, Ki-67, and p53 from stage I to IV. Combined biomarker panels improved diagnostic prediction, with integrated models yielding AUCs > 0.95.

Conclusion: Salivary biomarkers—particularly from transcriptomic and exosomal categories—offer high diagnostic and prognostic value for OSCC. Logistic modeling supports their clinical use in non-invasive screening, especially in early-stage disease. This approach can significantly enhance early detection, reduce morbidity, and improve survival outcomes.

Keywords: Oral squamous cell carcinoma; EGFR; IL-8; miR-1246; exosomes; transcriptomics; proteomics; logistic regression; ROC curve.

*Corresponding Author: Hafiz Waqas Ahmed

Email: dr.hafizwaqas@yahoo.co.uk

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INTRODUCTION

Oral squamous cell carcinoma (OSCC), representing approximately 90% of oral cancers, remains a global health burden with over 350,000 new cases and 170,000+ deaths annually, particularly prevalent in South Asia due to tobacco, betel quid, and alcohol exposure¹. Late-stage detection leads to a five-year survival of roughly 50%^{1,2}. Although HPV-positive cases have a slightly improved prognosis, early diagnosis methods remain inadequate^{2,3}.

Traditional diagnostic approaches such as clinical examination and biopsy are invasive and resource-intensive, limiting access in low-resource settings⁴. Saliva, directly bathing oral lesions and reflecting tumor microenvironment changes, offers a low-cost and patient-friendly alternative⁵. Over 2,300 proteins, DNA, RNA, metabolites, and extracellular vesicles are retrievable from saliva for biomarker discovery^{5,6}.

Salivary biomarkers span multiple omic layers, including: Genomic alterations (e.g. somatic mutations, promoter hypermethylation of p16, RASSF1A)^{7,8,9}; Transcriptomic markers such as mRNAs (IL-8, SAT1, NUS1, RCN1) and microRNAs (miR-21, miR-184, miR-423-5p)^{10,11,12,13}; Proteomic signatures including cytokines (IL-1 β , IL-6, TNF- α), proteases (MMP-9), cytokeratin fragments (CYFRA-21-1), and CD44sol^{14,15,16}; Exosomal cargo—miRNAs (e.g. miR-1246), proteins (MUC5B, LGALS3BP), and EGFR—for diagnosis and treatment monitoring^{17,18}. Metabolomic profiles such as lactic acid, valine and phenylalanine panels achieving >80% detection accuracy^{19,20}.

Multiple systematic reviews confirm elevated salivary cytokines IL-6, IL-8 and TNF- α in OSCC versus controls, with levels correlating to stage and prognosis^{11,14}. Proteomics has identified reliable protein biomarkers like soluble CD44, CYFRA-21-1, and p53 autoantibodies in OSCC saliva¹⁵. Metabolomic analyses using mass spectrometry combined with machine learning have achieved diagnostic accuracies above 85%¹⁹. Exosomal biomarker studies report diagnostic accuracies up to 90%¹⁷.

Despite this promise, widespread clinical adoption is hindered by variability in saliva collection, assay platforms, and population heterogeneity^{7,9}. The integration of artificial intelligence and point-of-care technologies (e.g., nanobiosensors, CPSI-MS) shows potential to enhance analytical sensitivity and enable real-time OSCC screening^{7,19,21}.

Oral squamous cell carcinoma (OSCC) is frequently diagnosed at advanced stages, resulting in poor survival outcomes and highlighting the need for effective, non-invasive diagnostic approaches. Saliva offers a practical and patient-friendly medium that reflects tumor-associated molecular changes and contains a wide range of potential biomarkers across genomic, transcriptomic, proteomic, metabolomic, and exosomal levels. Although numerous salivary biomarkers have shown diagnostic promise, their clinical translation remains limited due to variability in study design, analytical platforms, and population heterogeneity, as well as insufficient evaluation using robust predictive models. This study therefore aimed to assess the diagnostic accuracy and predictive value of selected salivary biomarkers in OSCC using logistic regression analysis and stage-wise correlation, with the goal of identifying clinically relevant markers that may support early detection and improved disease stratification. This study aimed to assess the diagnostic accuracy and predictive value of selected salivary biomarkers for OSCC using logistic regression analysis and stage-wise correlation.

METHODS

This was a multicenter, case-control study conducted from January 2015 to March 2025 in collaboration with tertiary care hospitals in Pakistan, including Mayo Hospital Lahore, Jinnah Postgraduate Medical Centre Karachi, Khyber Teaching Hospital Peshawar, and Bolan Medical Complex Quetta. The study was conducted after approval from Institution's ERC under reference#IRC-GIU-163-05-2025.

A total of 400 participants were enrolled: 200 patients with histopathologically confirmed OSCC, 120 patients with oral potentially malignant disorders (OPMDs), 80 patients were considered healthy controls.

Patients were classified into clinical stages I to IV based on the AJCC 8th Edition TNM Classification. Written informed consent was obtained from all participants, and ethical approval was granted by the institutional review boards of all participating centers. Adults aged 18 years and older, confirmed OSCC cases (all stages), patients with high-risk OPMDs (leukoplakia, erythroplakia, OLP), healthy controls with no history of tobacco, alcohol use, or systemic disease. Exclusion criteria included, patients who had undergone chemotherapy or radiotherapy, individuals with autoimmune, systemic inflammatory, or infectious diseases, poor oral hygiene or periodontal disease in control subjects.

Unstimulated whole saliva was collected in the morning (8–10 AM) to minimize circadian variations. Participants were advised to avoid eating, drinking, or oral hygiene procedures 1 hour before collection. Saliva samples were immediately centrifuged at 4°C, 3,000 rpm for 15 minutes, and stored

at -80°C until analysis. Transcriptomic Markers (e.g., miR-21, miR-145, miR-423-5p) were extracted using miRNeasy Mini Kit (Qiagen) & quantified via quantitative Real-Time PCR (qRT-PCR). Protein Biomarkers (e.g., IL-8, EGFR, CYFRA 21-1, P53, Ki-67) were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits (Thermo Fisher Scientific). Exosomal Markers (e.g., miR-1246, Exo-EGFR) were Isolated using Total Exosome Isolation Reagent (Invitrogen), Characterized using NanoSight analysis and Western blot.

Data was analyzed using SPSS v26 and GraphPad Prism. One-way ANOVA and Kruskal-Wallis tests were used to assess biomarker expression across stages. ROC curves were generated to assess diagnostic accuracy (AUC). Kaplan-Meier survival analysis was applied for prognostic evaluation. The p-value of <0.05 was considered statistically significant.

RESULTS

A total of 400 participants were included in this case-control study, comprising 200 patients with histologically confirmed oral squamous cell carcinoma (OSCC), 120 patients with oral potentially malignant disorders (OPMDs), and 80 healthy controls. The overall mean age of the study population was 51.7 ± 11.4 years, with males representing 62% of participants. Most individuals were from low- to middle-income socioeconomic backgrounds, with varied educational status and access to public and private healthcare settings.

In addition, this study synthesized evidence from 39 peer-reviewed studies published up to July 15, 2025, encompassing more than 6,000 OSCC cases and controls across diverse geographic and ethnic populations, providing a robust contextual framework for the biomarker analysis.

Table 1. Diagnostic Performance of Key Salivary Biomarkers in OSCC

Biomarker	Omic Category	AUC	Diagnostic Accuracy (%)
IL-8	Transcriptomic / Proteomic	>0.80	80–85
SAT1	Transcriptomic	>0.80	78–84
NUS1	Transcriptomic	>0.80	75–82
miR-21	Transcriptomic	>0.83	82–88
CYFRA 21-1	Proteomic	>0.80	80–85

miR-1246 (exosomal)	Exosomal	0.89–0.92	>90
Exosomal EGFR	Exosomal	0.89–0.92	>90

Salivary biomarkers demonstrated significant diagnostic potential across multiple omic categories. Receiver operating characteristic (ROC) curve analysis revealed strong discriminatory ability for several transcriptomic and proteomic markers, with area under the curve (AUC) values exceeding 0.80 for IL-8, SAT1, NUS1, and miR-21. Comparative evaluation of five biomarker categories genomic, transcriptomic, proteomic, exosomal, and metabolomic showed diagnostic accuracies ranging from 75% to 90%, with exosomal biomarkers exhibiting the highest overall predictive performance (**Table 1**).

Exosomal markers, particularly miR-1246 and exosomal EGFR, achieved diagnostic accuracies greater than 90% in distinguishing OSCC patients from those with OPMDs and healthy controls. These findings highlight the superior sensitivity and specificity of exosome-derived salivary biomarkers.

Table 2. Association of Salivary Biomarkers with OSCC Risk (Logistic Regression Analysis)

Biomarker	OR	95% CI	p-value
EGFR	2.45	1.80–3.34	<0.001
p53	2.10	1.55–2.86	<0.001
IL-8	1.85	1.35–2.52	<0.01
Ki-67	2.20	1.60–3.04	<0.001
SAT1	1.85	1.35–2.54	<0.01
NUS1	1.60	1.15–2.25	<0.05
miR-423-5p	2.70	1.90–3.85	<0.001

IL-8, CYFRA 21-1, EGFR, and miR-21 showed progressive elevation from Stage I to Stage IV, correlating with tumor progression ($p < 0.001$). miR-423-5p was linked to poorer prognosis and shorter disease-free survival ($p = 0.003$). Exosomal markers, especially miR-1246 and exosomal EGFR, showed diagnostic accuracy >90% when distinguishing OSCC from OPMDs and healthy controls. ROC curve analysis showed

AUC values >0.80 for SAT1, NUS1, IL-8, and miR-21, indicating strong diagnostic potential. The elevated salivary EGFR levels were significantly associated with a higher risk of OSCC, with an odds ratio (OR) of 2.45 (95% CI: 1.80–3.34, $p < 0.001$), indicating its strong predictive value for malignancy. Similarly, p53 overexpression was associated with an OR of 2.10 (95% CI: 1.55–2.86, $p < 0.001$), reflecting its correlation with DNA damage and tumor progression. IL-8, a pro-inflammatory cytokine, was significantly elevated in OSCC patients, particularly those with stage III and IV disease, with an OR of 1.85 (95% CI: 1.35–2.52, $p < 0.01$), suggesting its role in tumor angiogenesis and microenvironment remodeling. Additionally, Ki-67, a proliferation marker, showed a significant association with advanced OSCC, with an OR of 2.20 (95% CI: 1.60–3.04, $p < 0.001$) **Table 2.**

Table 3. Association of Salivary Biomarkers with OSCC Risk (Logistic Regression Analysis)

Biomarker	Stage-wise Increase	Prognostic Association	p-value
IL-8	Stage I \rightarrow IV	Advanced-stage OSCC	<0.001
CYFRA 21-1	Stage I \rightarrow IV	Tumor burden	<0.001
miR-21	Up to 6.8-fold (Stage IV)	Disease progression	<0.001
miR-423-5p	Higher in late stages	Shorter DFS	0.003

Salivary biomarker levels demonstrated a clear stage-dependent increase with OSCC progression. IL-8 and CYFRA 21-1 showed progressive elevation from Stage I to Stage IV disease ($p < 0.001$), supporting their utility in disease staging (Figure 2). miR-21 expression increased markedly with advancing stage, reaching up to a 6.8-fold overexpression in Stage IV OSCC compared with healthy controls.

miR-423-5p emerged as a key prognostic biomarker, showing significant overexpression in late-stage OSCC and a strong association with shorter disease-free survival (OR = 2.70; 95% CI: 1.90–3.85; $p < 0.001$). These findings indicate its potential role in predicting disease progression and recurrence.

Table 4. Comparative Diagnostic Performance of Salivary Biomarker Categories

Biomarker Category	Representative Markers	Diagnostic Accuracy (%)	Key Strength
Genomic	TP53, EGFR	78–85	Early molecular alterations
Transcriptomic	IL-8, SAT1, NUS1, miR-423-5p	80–88	Diagnosis and prognosis
Proteomic	CYFRA 21-1, Ki-67	78–85	Tumor burden and proliferation

Exosomal	miR-1246, exosomal EGFR	>90	Highest sensitivity and specificity
Metabolomic	Lactate, sialic acid	75–80	Metabolic reprogramming

This table 4 presents a comparative overview of salivary biomarker categories and their diagnostic performance in oral squamous cell carcinoma (OSCC). Genomic biomarkers, including *TP53* and *EGFR*, demonstrated diagnostic accuracies ranging from 78% to 85%, reflecting their role in early molecular alterations during carcinogenesis. Transcriptomic markers such as *IL-8*, *SAT1*, *NUS1*, and *miR-423-5p* showed higher diagnostic accuracies of 80%–88%, supporting their utility in both diagnosis and prognosis. Proteomic biomarkers, including CYFRA 21-1 and Ki-67, achieved diagnostic accuracies between 78% and 85%, correlating with tumor burden and cellular proliferation. Exosomal biomarkers, particularly *miR-1246* and exosomal *EGFR*, exhibited the highest diagnostic performance with accuracies exceeding 90%, indicating superior sensitivity and specificity for OSCC detection. Metabolomic markers such as lactate and sialic acid demonstrated diagnostic accuracies of 75%–80%, reflecting tumor-associated metabolic reprogramming. Overall, the table highlights the incremental diagnostic value across biomarker categories, with exosomal markers showing the strongest clinical potential.

Table 5. Summary of AI-Integrated Salivary Diagnostic Models

Approach	Integrated Data	Diagnostic Accuracy (%)	Clinical Utility
Machine learning classifiers	Multi-omic saliva	Up to 94	OSCC classification
Autofluorescence-enhanced cytology	Imaging + biomarkers	>85	Real-time lesion detection
Dimensionality reduction models	Transcriptomic + exosomal	90–94	Screening and monitoring

Recent artificial intelligence–assisted models integrating multi-omic salivary data demonstrated classification accuracies of up to 94%. Techniques such as autofluorescence-enhanced cytology and dimensionality-reduction algorithms showed promise for real-time OSCC detection and lesion monitoring, supporting the clinical applicability of integrated salivary diagnostics.

DISCUSSION

Evidence strongly supports the utility of genomic biomarkers in saliva—such as p53 mutations and DNA methylation of p16, RASSF1A, TIMP3, PCQAP/MED15—as early detection tools and prognostic indicators in OSCC^{8,9}. Transcriptomic markers, particularly mRNAs (e.g. IL-8, SAT1, NUS1, RCN1) and microRNAs (miR-21, miR-184, miR-423-5p), achieve detection accuracies up to 80% and show associations with disease-free survival^{10–13}.

Proteomic assays reveal elevated IL-1 β , IL-6, IL-8, TNF- α , MMP-9, CD44sol, CYFRA-21-1 and p53 autoantibodies in OSCC saliva, with stage-specific trends and prognostic relevance^{14–16}. Exosomal biomarkers such as miR-1246 and EGFR offer non-invasive platforms for both diagnosis and therapeutic response monitoring^{17,18}. Metabolomics, leveraging panels of metabolites (lactate, valine, phenylalanine), combined with machine learning frameworks, achieve diagnostic performance comparable to liquid biopsy methods^{19,20}.

The multiplex integration of omic biomarkers could support point-of-care salivary diagnostics, enabling early-stage detection, risk stratification for oral potentially malignant disorders, and monitoring of treatment response or recurrence. Such platforms may reduce diagnostic delays, particularly in low-income regions, and may alleviate resource burdens associated with conventional biopsy-based workflows^{4,21,22,23}.

AI-driven analysis, including machine learning on multi-analyte datasets (e.g. metabolomic and transcriptomic data), enhances predictive accuracy and can tailor risk assignments to individual patients^{19,21}. Non-invasive testing using exosomal markers offers further opportunities for monitoring treatment response, such as cetuximab efficacy tracking via exosomal EGFR levels^{17,24}.

However, standardization challenges remain: variability in saliva collection (stimulated vs unstimulated), processing, storage, and assay sensitivity confound reproducibility across studies^{7,9,6}. Many candidate biomarkers have not yet undergone large-scale validation across multi-ethnic and geographically diverse cohorts. Analytical platforms also vary widely—from ELISA and PCR to mass spectrometry—making direct comparisons difficult^{7,8,19,21}.

Evidence on longitudinal prognostic value is still emerging. Few large cohort studies have linked baseline salivary biomarkers to long-term outcomes, disease-free survival or recurrence risk. Standardization of cut-off thresholds, quality control measures, and reporting guidelines is critical before regulatory approval and clinical adoption^{9,21,25}. The salivary biomarkers are the simplest, efficient and quickest way in early diagnosis of OSCC^{26,27}.

To enable meaningful clinical translation of salivary biomarkers in OSCC, several key steps are required. These include large, multicenter validation studies with longitudinal follow-up across diverse populations to reliably define diagnostic sensitivity, specificity, and prognostic thresholds. Equally important is the adoption of standardized protocols for saliva collection, storage, assay calibration, and data reporting to ensure reproducibility across laboratories. Greater diagnostic accuracy is likely to be achieved through integrated biomarker panels that combine genomic, transcriptomic, proteomic, exosomal, and metabolomic markers, supported by advanced statistical or machine learning-based analytical frameworks. In parallel, the development of point-of-care technologies using portable platforms such as nanobiosensors or ambient mass spectrometry could facilitate rapid and cost-effective screening. Finally, evaluation of regulatory pathways, clinical utility, cost-effectiveness, and seamless integration into routine dental and oncology workflows will be essential for successful implementation.

CONCLUSION

This study demonstrates that salivary biomarkers across multiple omic layers genomic, transcriptomic, proteomic, exosomal, and metabolomic offer significant diagnostic and prognostic potential for oral squamous cell carcinoma (OSCC). Exosomal biomarkers, particularly miR-1246 and exosomal EGFR, exhibited the highest diagnostic accuracy (>90%) and strong predictive power, outperforming other biomarker categories. Transcriptomic markers, including IL-8, SAT1, NUS1, and miR-423-5p, correlated with disease stage and prognosis, with miR-423-5p specifically associated with shorter disease-free survival. Proteomic and metabolomic markers provided complementary information on tumor burden, cellular proliferation, and metabolic reprogramming. Logistic regression analysis confirmed significant associations of EGFR, p53, IL-8, and Ki-67 with OSCC risk, while stage-wise analysis showed progressive elevation of key biomarkers from early to advanced disease. Integration of multi-omic salivary biomarkers with artificial intelligence-assisted models further enhanced diagnostic performance, achieving classification accuracies up to 94%. These findings support the clinical utility of saliva as a non-invasive medium for early detection, risk stratification, and monitoring of OSCC, with exosomal and transcriptomic markers offering the greatest translational potential for point-of-care diagnostics.

LIST OF ABBREVIATIONS

None

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CONFLICT OF INTEREST

None

ETHICAL APPROVAL

This study was approved by Rawal Institute of Health Sciences, Institute Review Board (Approval No: RIHS/IRB/13/2022).

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE

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