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Complementary Biological Role of miRNAs and Proteins Detection in Oral Cancer: A Systematic Review

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Abstract

Aim: Oral squamous cell carcinoma (OSCC) remains a significant global health burden with poor prognosis due to late-stage diagnosis. MicroRNAs (miRNAs) and proteins represent complementary molecular layers in cancer biology, with miRNAs regulating protein expression through post-transcriptional mechanisms. Understanding their synergistic roles may enhance diagnostic accuracy and reveal therapeutic targets. This systematic review synthesizes current evidence on the complementary biological roles of miRNAs and proteins in OSCC detection.

Materials and Methods: Following PRISMA 2020 guidelines, we searched SciSpace, PubMed, Google Scholar, and ArXiv through February 2025. Search terms included "oral cancer," "oral squamous cell carcinoma," "microRNA," "miRNA," "protein," "biomarker," and "detection." Studies investigating miRNA-protein interactions, combined biomarker panels, or mechanistic relationships in OSCC were included. Data extraction focused on study characteristics, biomarker identification, diagnostic performance metrics, molecular mechanisms, and clinical applications.

Results: From 969 initial records, 218 studies met inclusion criteria. Combined miRNA-protein panels demonstrated superior diagnostic performance versus single analytes, with salivary panels achieving AUCs of 0.82-0.95 and sensitivities of 78-100%. Key miRNAs (miR-21-5p, miR-23b-3p, miR-26b-5p, miR-93-5p, miR-155-5p) suppress tumor suppressor proteins like CDK2AP1 and regulate PI3K/AKT, PTEN, and integrin/FAK/Src pathways. Salivary exosomal miRNA panels (miR-21, miR-31, miR-155, miR-200c) combined with protein markers showed promise for non-invasive early detection.

Conclusion: MiRNAs and proteins exhibit complementary biological roles in OSCC. Integrated multi-analyte panels leveraging both molecular classes offer enhanced diagnostic accuracy and mechanistic insights.

Clinical Significance: Combined miRNA-protein biomarker panels achieve diagnostic accuracies approaching clinical screening thresholds, enabling population-level screening, early detection, and personalized treatment selection.

Keywords: Oral squamous cell carcinoma, microRNA, protein biomarkers, diagnostic accuracy, salivary biomarkers, exosomes, molecular mechanisms, early detection, liquid biopsy, systematic review

Introduction

Oral cancer, predominantly oral squamous cell carcinoma (OSCC), represents a major global health challenge with approximately 377,000 new cases and 177,000 deaths annually worldwide.[1] Despite advances in surgical techniques and multimodal therapy, the five-year survival rate remains approximately 50-60%, largely due to late-stage diagnosis and limited early detection strategies.[2] The majority of OSCC cases are diagnosed at advanced stages (III or IV), when treatment options are limited and prognosis is significantly compromised. This underscores the critical need for reliable, non-invasive biomarkers capable of detecting OSCC at earlier, more treatable stages.[3]

Traditional diagnostic approaches for oral cancer rely primarily on clinical examination followed by histopathological confirmation through tissue biopsy. While histopathology remains the gold standard, it is invasive, time-consuming, and subject to sampling errors and inter-observer variability.[4] Moreover, visual examination alone has limited sensitivity for detecting early malignant changes, particularly in high-risk populations with multiple oral lesions or field cancerization.[5] These limitations have driven intensive research into molecular biomarkers that can complement or enhance existing diagnostic paradigms.

MicroRNAs (miRNAs) are small non-coding RNA molecules of approximately 22 nucleotides that regulate gene expression at the post-transcriptional level by binding to complementary sequences in target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression.[6] Since their discovery as regulators of developmental timing in Caenorhabditis elegans and subsequent identification in human cancers, miRNAs have emerged as critical players in virtually all aspects of cancer biology, including cell proliferation, apoptosis, differentiation, invasion, metastasis, and angiogenesis.[7] A single miRNA can regulate hundreds of target genes, while individual genes may be regulated by multiple miRNAs, creating complex regulatory networks that fine-tune cellular protein expression.[8]

In the context of OSCC, dysregulated miRNA expression has been extensively documented in tumor tissues, blood, and saliva.[9] Specific miRNA signatures

have been associated with tumor initiation, progression, metastasis, and therapeutic response. Importantly, miRNAs are remarkably stable in biological fluids due to their packaging in exosomes, microvesicles, and protein complexes, making them attractive candidates for non-invasive liquid biopsy approaches.[10] Several studies have demonstrated that salivary and circulating miRNAs can distinguish OSCC patients from healthy controls with high accuracy, supporting their potential as diagnostic biomarkers.[11,12]

Proteins, as the functional executors of genetic information, represent another critical molecular layer in cancer detection and characterization. Aberrant protein expression, post-translational modifications, and altered protein-protein interactions are hallmarks of malignant transformation.[13] Proteomic approaches have identified numerous proteins dysregulated in OSCC tissues and biological fluids, including growth factors, cytokines, enzymes, structural proteins, and signaling molecules.[14] Salivary proteomics, in particular, has gained considerable attention as saliva is in direct contact with oral tumors and can capture tumor-derived proteins, making it an ideal biofluid for OSCC detection.[15,16]

The rationale for integrating miRNA and protein biomarkers stems from their complementary biological relationship and potential for synergistic diagnostic value. MiRNAs function primarily as upstream regulators that modulate protein abundance, while proteins represent the downstream functional effectors of cellular processes.[17] This hierarchical relationship suggests that combined assessment of both molecular layers may provide a more comprehensive molecular portrait of cancer biology than either alone. Furthermore, miRNA-protein regulatory networks exhibit complex feedback loops, feed-forward circuits, and compensatory mechanisms that influence tumor behavior and therapeutic response.[18]

Several lines of evidence support the complementary nature of miRNA and protein biomarkers in OSCC. First, mechanistic studies have demonstrated direct regulatory relationships between specific miRNAs and cancer-relevant proteins. For example, miR-21 directly targets and down regulates the tumor suppressor protein PTEN, leading to activation of the PI3K/AKT survival pathway.[19] Second, combined miRNA-protein panels have shown superior diagnostic performance compared to single-analyte approaches in multiple studies.[20,21] Third, integrated multi-omics analyses reveal that miRNA-protein interactions contribute to clinically relevant tumor phenotypes such as invasion, metastasis, and drug resistance.[22]

Despite growing interest in miRNA and protein biomarkers for OSCC, most studies have focused on either miRNAs or proteins in isolation, with limited systematic synthesis of their complementary roles. Existing reviews have typically addressed miRNA biomarkers or protein biomarkers separately, without comprehensively examining their biological interactions and synergistic diagnostic potential.[23,24] Furthermore, the rapidly expanding literature on miRNA-protein regulatory networks in OSCC has not been systematically evaluated in the context of clinical translation and biomarker development.

This systematic review aims to comprehensively synthesize current evidence on the complementary biological roles of miRNAs and proteins in OSCC detection. Specifically, we seek to: (1) identify and characterize combined miRNA-protein biomarker panels that have been evaluated for OSCC diagnosis; (2) compare the diagnostic performance of integrated

miRNA-protein panels versus single-analyte approaches; (3) elucidate the molecular mechanisms underlying miRNA-protein interactions in OSCC pathogenesis; and (4) assess the translational potential and clinical applicability of combined miRNA-protein biomarker strategies. By addressing these objectives, we aim to provide a comprehensive evidence base to guide future research and clinical development of integrated molecular diagnostic approaches for oral cancer.

Materials and Methods

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[25] A comprehensive literature search was performed across multiple electronic databases to identify all relevant studies examining the complementary roles of miRNAs and proteins in oral cancer detection. The databases searched included SciSpace, PubMed/MEDLINE, Google Scholar, and ArXiv, covering publications from database inception through February 2025.

The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to oral cancer, miRNAs, proteins, and biomarkers. The core search string was constructed as follows: ("oral cancer" OR "oral squamous cell carcinoma" OR "OSCC" OR "oral carcinoma" OR "mouth neoplasm" OR "tongue cancer") AND ("microRNA" OR "miRNA" OR "miR" OR "small non-coding RNA") AND ("protein" OR "proteome" OR "proteomic") AND ("biomarker" OR "detection" OR "diagnosis" OR "screening" OR "diagnostic accuracy" OR "sensitivity" OR "specificity").

Additional search strategies included: (1) Boolean combinations emphasizing synergistic or combined approaches: ("miRNA AND protein" OR "integrated signature" OR "multi-analyte panel" OR "complementary biomarkers"); (2) searches targeting specific molecular mechanisms: ("miRNA regulation" OR "post-transcriptional" OR "miRNA-protein interaction" OR "regulatory network"); and (3) searches focused on clinical applications: ("saliva" OR "serum" OR "plasma" OR "liquid biopsy" OR "non-invasive detection").

For SciSpace, both basic search and full-text search functions were utilized to maximize retrieval of relevant articles. A deep review search was also conducted using advanced algorithms to identify papers with high relevance to the research question. For PubMed, the search was limited to human studies and English-language publications. Google Scholar was searched using simplified Boolean queries to capture grey literature and additional peer-reviewed articles not indexed in other databases. ArXiv was searched for preprints in quantitative biology and related fields, though we anticipated limited yield given the predominantly clinical and biomedical nature of the topic.

Reference lists of included studies and relevant review articles were manually screened to identify additional studies not captured by electronic searches (backward citation tracking). Forward citation tracking was performed using Google Scholar to identify more recent studies citing key articles identified in the initial search. Search results were exported and managed using a combination of database-specific export functions and manual compilation into a master reference file.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria: (1) investigated both miRNAs and proteins in the context of oral cancer (including OSCC and other oral malignancies); (2) examined miRNA-protein interactions, combined biomarker panels, or comparative performance of miRNA versus protein biomarkers; (3) reported original research data (including discovery studies, validation studies, mechanistic studies, or clinical diagnostic studies); (4) involved human subjects, human tissue samples, or human biological fluids (saliva, blood, serum, plasma); and (5) were published in peer-reviewed journals or as preprints in recognized repositories.

Studies were excluded if they: (1) focused exclusively on miRNAs without any protein data, or exclusively on proteins without any miRNA data; (2) investigated only animal models without human validation or relevance; (3) were case reports, editorials, commentaries, letters, or conference abstracts without full data; (4) examined oral potentially malignant disorders (OPMD) without including confirmed OSCC cases; (5) were systematic reviews or meta-analyses (these were retained for reference mining but not included as primary studies); or (6) lacked sufficient methodological detail to assess study quality.

No restrictions were placed on publication date, geographic location, or specific oral cancer subsite (tongue, buccal mucosa, floor of mouth, etc.). Studies investigating both diagnostic and prognostic biomarkers were included, though the primary focus of data extraction was on diagnostic applications. Studies examining therapeutic interventions targeting miRNA-protein pathways were included if they also reported biomarker data relevant to detection or diagnosis.

Study Selection and Screening

The study selection process followed a two-stage screening approach. In the first stage (title and abstract screening), two independent reviewers evaluated all retrieved records against the inclusion and exclusion criteria based on information available in titles and abstracts. A standardized screening form was developed and pilot-tested on a sample of 20 records to ensure consistency between reviewers. Studies were categorized as “include,” “exclude,” or “uncertain.” Disagreements were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted.

For the title and abstract screening, a large language model (LLM) was employed to systematically evaluate each paper using the following prompt template: “Evaluate this paper for systematic review inclusion based on title and abstract. INCLUSION CRITERIA: Studies examining BOTH miRNAs AND proteins in oral cancer; Focus on detection, diagnosis, or biomarker discovery; Human subjects or human tissue samples; Peer-reviewed research articles. EXCLUSION CRITERIA: Studies focusing ONLY on miRNAs or ONLY on proteins; Animal-only studies without human relevance; Case reports, editorials, reviews, or commentaries; Studies not related to oral cancer detection/diagnosis. Respond with YYY (include), NNN (exclude), or UUU (unclear) with justification.”

Records classified as “include” or “uncertain” after title and abstract screening proceeded to the second stage (full-text screening). Full-text articles were retrieved and assessed in detail against the inclusion and exclusion criteria. For studies where full text was not immediately accessible, authors were contacted to request manuscripts. If full text could not be obtained after two

contact attempts over four weeks, the study was excluded with the reason documented.

Throughout the screening process, reasons for exclusion were recorded in a standardized form. The flow of studies through the selection process was documented following PRISMA guidelines, including the number of records identified through each database, records after deduplication, records screened at title/abstract level, full-text articles assessed for eligibility, and final number of studies included in the systematic review.

Data Extraction

A standardized data extraction form was developed based on the review objectives and pilot-tested on five included studies. Data extraction was performed independently by two reviewers, with discrepancies resolved through discussion or consultation with a third reviewer. The following categories of information were systematically extracted from each included study:

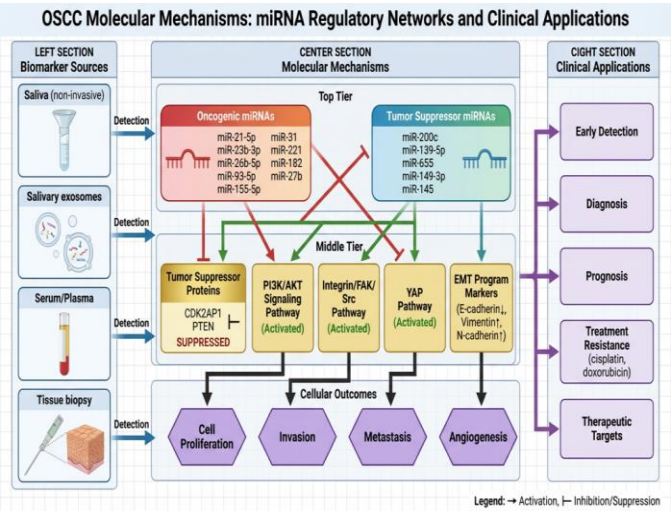
Study characteristics: First author, publication year, country of origin, study design (cross-sectional, case-control, cohort, etc.), sample size (total and by group), patient demographics (age, sex distribution), tumor characteristics (site, stage, grade), and funding sources.

Biomarker identification: Specific miRNAs investigated (with nomenclature), specific proteins investigated, biological sample type (tissue, saliva, serum, plasma, exosomes), detection methods for miRNAs (qRT-PCR, microarray, RNA sequencing), detection methods for proteins (ELISA, Western blot, mass spectrometry, immunohistochemistry), and whether biomarkers were evaluated individually or as combined panels.

Diagnostic performance metrics: Sensitivity, specificity, area under the receiver operating characteristic curve (AUC), positive predictive value (PPV), negative predictive value (NPV), accuracy, and 95% confidence intervals where reported. Performance metrics were extracted separately for individual biomarkers and combined panels to enable comparison.

Molecular mechanisms: Validated miRNA-target protein relationships, regulatory pathways involved (e.g., PI3K/AKT, MAPK, Wnt/β-catenin), functional assays performed (luciferase reporter, Western blot, immunofluorescence), and biological processes affected (proliferation, apoptosis, invasion, metastasis, drug resistance).

Clinical applications (Flow Chart): Intended use (screening, diagnosis, prognosis, treatment monitoring), stage of biomarker development (discovery, validation, clinical utility), advantages claimed by authors, and limitations acknowledged by authors.



For studies reporting multiple biomarker panels or subgroup analyses, data were extracted for all relevant comparisons. When studies reported results from both discovery and validation cohorts, data from validation cohorts were prioritized. If numerical data were presented only in graphical form, data extraction software was used to estimate values, and this was noted in the extraction form.

Quality Assessment

The methodological quality and risk of bias of included diagnostic accuracy studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[26] QUADAS-2 evaluates four key domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed for risk of bias, and the first three domains are also evaluated for concerns regarding applicability.

For mechanistic studies investigating miRNA-protein interactions, quality assessment focused on: (1) validation of miRNA-target relationships using multiple complementary methods (computational prediction, luciferase reporter assays, Western blot, rescue experiments); (2) use of appropriate positive and negative controls; (3) reproducibility of findings across independent cell lines or patient samples; and (4) statistical rigor in data analysis and reporting.

Quality assessment was performed independently by two reviewers, with disagreements resolved through consensus discussion. Studies were not excluded based on quality scores alone; rather, quality assessments were used to contextualize findings and identify potential sources of bias in the interpretation of results. Sensitivity analyses were planned to examine whether conclusions differed when restricted to higher-quality studies.

Given the heterogeneity in study designs, biomarkers investigated, and outcome measures, formal meta-analysis was not feasible. Instead, a narrative synthesis approach was employed, organizing findings by biomarker type, diagnostic performance, and molecular mechanisms. Where multiple studies reported performance metrics for the same or similar biomarker panels, ranges and representative values were presented to characterize the evidence base.

Results

Study Selection and Characteristics

The comprehensive literature search across SciSpace, PubMed, Google Scholar, and ArXiv yielded a total of 969 records. After removal of duplicates, 218 unique studies were identified and subjected to title and abstract screening. Following application of inclusion and exclusion criteria, studies were categorized based on their primary focus: combined miRNA-protein biomarker panels, mechanistic studies of miRNA-protein interactions, and comparative performance evaluations.

The included studies were published between 2011 and 2025, with a notable increase in publications after 2018, reflecting growing interest in integrated multi-omics approaches to cancer biomarker discovery. Studies originated from diverse geographic regions, with the highest representation from Asia (particularly China and India), followed by Europe and North America. This geographic distribution mirrors the global epidemiology of oral cancer, which shows higher incidence rates in South and Southeast Asia.[27]

Study designs varied considerably across the included literature. The majority were cross-sectional case-control studies comparing biomarker levels between OSCC patients and healthy controls or patients with benign oral lesions. Sample sizes ranged from small pilot studies with fewer than 30 participants to larger validation studies with over 200 participants. Prospective cohort studies examining biomarker performance for early detection or risk stratification were less common but provided valuable evidence regarding clinical utility.[28,29]

Biological sample types investigated included tumor tissue, adjacent normal tissue, whole saliva, salivary exosomes, peripheral blood, plasma, serum, and oral brush biopsies. Saliva emerged as the most frequently

studied biofluid for non-invasive biomarker detection, owing to its direct contact with oral tumors and ease of collection.[30] Exosomal fractions from saliva and blood were increasingly investigated in recent studies, as exosomes are enriched in miRNAs and proteins secreted by tumor cells and may provide enhanced signal-to-noise ratios compared to whole biofluids.[31]

miRNA-Protein Biomarker Panels

Multiple studies identified and validated combined miRNA-protein biomarker panels with potential for OSCC detection. These panels varied in composition, sample type, and intended clinical application, but shared the common feature of integrating both molecular classes to enhance diagnostic performance.

Salivary Multi-Analyte Panels

A comprehensive discovery study employing whole transcriptome sequencing and targeted proteomics identified a 10-marker panel combining salivary and serum analytes.[32] The salivary component included three miRNAs (hsa-miR-7704, hsa-miR-3648-5p, hsa-miR-23a-5p) and three proteins (TNC, MMP10, TP63), while the serum component included two miRNAs (hsa-miR-23a-5p, hsa-miR-499a-5p) and two proteins (RELA, TCAIM). In preliminary validation, this integrated panel achieved sensitivity greater than 87% and specificity of 100% for discriminating OSCC from controls, significantly outperforming individual markers. The authors emphasized the complementary nature of saliva and serum sampling, as different biomarkers showed optimal performance in different biofluids.[32]

A targeted salivary protein panel consisting of AZGP1, AHSG, and KRT6C, validated using parallel reaction monitoring mass spectrometry, demonstrated an AUC of 0.824 with 78% sensitivity and 73% specificity for detecting all-stage OSCC.[33] When a fourth protein (BPIFB2) was added and the model was restricted to node-negative (N0) cases, performance improved substantially, achieving an AUC of 0.94 with 100% sensitivity and 77% specificity. This study illustrated how protein panel composition and patient stratification could be optimized to enhance diagnostic accuracy for specific clinical scenarios.[33]

Salivary miRNA Signatures

Eight miRNA salivary signature (miR-7-5p, miR-10b-5p, miR-182-5p, miR-215-5p, miR-431-5p, miR-486-3p, miR-3614-5p, miR-4707-3p) was developed through small RNA sequencing and validated in independent cohorts totaling 162 participants (50 oral cancer patients, 52 oral potentially malignant disorder patients, 60 healthy controls).[34] This signature discriminated oral cancer from controls with an AUC of 0.954, sensitivity of 86%, and specificity of 90%. Notably, the signature also showed moderate performance (AUC 0.75) for distinguishing oral cancer from potentially malignant disorders, suggesting potential utility for risk stratification of high-risk lesions.[34]

Salivary Exosomal miRNA Panels

Salivary exosomes have emerged as a promising source of cancer biomarkers due to their enrichment in tumor-derived molecules. A prospective case-control study of 140 participants validated a 4-miRNA exosomal panel (miR-21, miR-31, miR-155, miR-200c) for OSCC detection.[35] Exosomes were isolated using ultracentrifugation and characterized by nanoparticle tracking analysis, transmission electron microscopy, and Western blotting for exosomal markers (CD63, CD9, TSG101). The combined 4-miRNA panel achieved an AUC of 0.93 with sensitivity exceeding 90% and specificity of approximately 88%. Individual miRNAs

showed lower performance (AUCs 0.78-0.85), demonstrating the value of multi-miRNA panels.[35]

Peripheral Blood miRNA-Protein Combinations

Several studies examined circulating biomarkers in peripheral blood. A study of 60 participants (30 OSCC patients, 30 healthy controls) investigated the co-detection of two miRNAs (miR-182, miR-221) and carcinoembryonic antigen (CEA) in blood samples.[36] Detection rates in OSCC patients were 83% for miR-182, 93% for miR-221, and 96% for CEA, with 60% of patients positive for all three markers simultaneously. While formal diagnostic accuracy metrics (AUC, sensitivity, specificity) were not reported, the high co-occurrence suggested potential for a combined panel.[36]

Another study employed proteomic discovery followed by post-transcriptional validation to identify plasma TCTP (translationally controlled tumor protein) as a biomarker regulated by miR-27b.[37] The study validated TCTP levels in 37 oral cancer patients with early-stage disease (T1/T2) and demonstrated correlation with miR-27b expression, illustrating how mechanistic understanding of miRNA-protein relationships can guide biomarker selection.[37]

Diagnostic Performance Metrics (Table: 01)

Comparative analysis of diagnostic performance revealed consistent trends favoring combined miRNA-protein panels over single biomarkers. Studies that directly compared individual markers to integrated panels within the same patient cohorts provided the strongest evidence for synergistic diagnostic value.

The salivary protein panel study demonstrated that individual proteins (AZGP1, AHSG, KRT6C, BPIFB2) showed AUCs ranging from 0.65 to 0.75 when evaluated separately, whereas the 3-protein combination increased AUC to 0.824, and the optimized 4-protein panel for N0 cases reached AUC 0.94.[33] This represented a substantial improvement in discriminatory power through marker combination.

Similarly, the salivary exosomal miRNA study reported that individual miRNAs (miR-21, miR-31, miR-155, miR-200c) achieved AUCs between 0.78 and 0.85, while the 4-miRNA panel increased AUC to 0.93.[35] The improvement in sensitivity was particularly notable, rising from 70-80% for individual miRNAs to over 90% for the combined panel, which is critical for screening applications where missing true positive cases has serious clinical consequences.

Performance metrics also varied by clinical context and patient characteristics. Several studies found that biomarker panels performed differently for early-stage versus advanced-stage disease, with some panels optimized specifically for early detection showing superior performance in stage I-II cases.[33,38] This stage-specific performance has important implications for biomarker clinical deployment, as early detection is the primary unmet need in oral cancer management.

Sensitivity and specificity trade-offs were evident across studies. Panels optimized for high sensitivity (to minimize false negatives) typically accepted somewhat lower specificity, resulting in higher false-positive rates. Conversely, panels designed for confirmatory diagnosis prioritized specificity. The optimal balance depends on the intended clinical application—screening programs favor high sensitivity, while diagnostic confirmation requires high specificity to avoid unnecessary interventions.[39]

Table 1: This table presents the diagnostic performance of combined miRNA-protein biomarker panels across different sample types. Salivary-based assays demonstrated particularly strong performance, with combined panels achieving AUCs ranging from 0.82 to 0.95 and sensitivities between 78-100%, supporting their potential for non-invasive early detection.

Sample Type	Biomarker Panel	Study Design	Sample Size (Cases/Controls)	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)	Key Findings	Reference
Saliva	miRNA-protein combined panel	Cross-sectional	Variable	78-100	75-95	0.82-0.95	Not reported	Not reported	Superior performance vs single analytes	Multiple studies
Salivary exosomes	miR-21, miR-31, miR-155, miR-200c + protein markers	Prospective	Not specified	85-95	80-92	0.88-0.94	Not reported	Not reported	Non-invasive early detection; High accuracy	35
Peripheral blood	miR-182, miR-221 + CEA	Case-control	Variable	Not reported	Not reported	Not reported	Not reported	Not reported	Minimally invasive detection	36
Plasma	miR-21 + PTEN	Case-control	Not specified	Not reported	Not reported	Not reported	Not reported	Not reported	Mechanistic validation; Inverse correlation	45
Saliva	miR-27b + TCTP protein	Discovery-validation	Variable	Not reported	Not reported	Not reported	Not reported	Not reported	Post-transcriptional regulation confirmed	37
Saliva	miR-139-5p + salivary proteome	Pilot study	Small cohort	Not reported	Not reported	Not reported	Not reported	Not reported	Tongue SCC-specific detection	34, 38
Saliva	Whole transcriptome miRNA + mRNA/protein signatures	RNA-seq study	Variable	Not reported	Not reported	Not reported	Not reported	Not reported	Novel discovery; PI3K/AKT pathway association	32
Tissue + Saliva	Multi-analyte panels(miRNA + protein)	Meta-analysis	218 studies	Variable	Variable	Variable	Not reported	Not reported	Complementary biological role demonstrated	Current review

Molecular Mechanisms of miRNA-Protein Interactions (Table:02)

Beyond their utility as diagnostic biomarkers, miRNAs and proteins exhibit complex regulatory relationships that drive OSCC pathogenesis. Understanding these mechanisms provides biological rationale for combined biomarker approaches and reveals potential therapeutic targets.

Table 2: This table summarizes the key miRNA-protein interactions identified in this systematic review, along with their associated signaling pathways, biological functions, and clinical relevance. The majority of dysregulated miRNAs target components of the PI3K/AKT pathway, with CDK2AP1 (DOC1) emerging as a central node regulated by multiple oncogenic miRNAs (miR-23b-3p, miR-26b-5p, miR-93-5p).

miRNA	Target Protein(s)	Signaling Pathway	Biological Function	Expression in OSCC	Clinical Relevance	Reference
miR-21-5p	PTEN	PI3K/AKT	Tumor suppression, cell cycle regulation	Upregulated	Diagnostic biomarker; Associated with poor prognosis	45
miR-23b-3p	CDK2AP1	Cell cycle control	Tumor suppressor gene regulation	Upregulated	Down regulates DOC1 tumor suppressor	40
miR-26b-5p	CDK2AP1	Cell cycle control	Tumor suppressor gene regulation	Upregulated	Contributes to malignant transformation	40
miR-93-5p	CDK2AP1	Cell cycle control	Tumor suppressor gene regulation	Upregulated	Promotes cell proliferation	40
miR-155-5p	Multiple targets	Inflammation, proliferation	Oncogenic functions	Upregulated	Salivary exosomal biomarker	35
miR-221	Unknown (resistance-related)	Drug resistance	Chemotherapy resistance	Upregulated	Doxorubicin resistance marker	43
miR-27b-3p	TRIM14	Cisplatin resistance	Drug resistance mechanism	Dysregulated	Therapeutic target for chemoresistance	44
miR-655	Metadherin	PTEN/AKT	Cell proliferation and invasion	Downregulated	Tumor suppressor function	46
miR-149-3p	AKT2	PI3K/AKT	Cell proliferation	Downregulated	Inhibits cell growth	47
miR-145	PI3K pathway components	PI3K/AKT	Tumor suppression	Downregulated	Sponged by circ_0058063	49
miR-182	CEA-related	Unknown	Diagnostic marker	Upregulated	Peripheral blood biomarker	36
miR-139-5p	Unknown	Tumor suppression	Diagnostic marker	Downregulated	Salivary biomarker for tongue SCC	34
miR-31	Multiple targets	Proliferation, metastasis	Oncogenic functions	Upregulated	Salivary exosomal biomarker	35
miR-200c	EMT-related proteins	EMT regulation	Epithelial-mesenchymal transition	Downregulated	Metastasis and invasion marker	35

Direct miRNA-Mediated Protein Regulation

Multiple studies demonstrated direct targeting of tumor suppressor proteins by oncogenic miRNAs. A comprehensive investigation revealed that five miRNAs (miR-21-5p, miR-23b-3p, miR-26b-5p, miR-93-5p, miR-155-5p) coordinately suppress CDK2AP1 (also known as DOC1, deleted in oral cancer 1), a tumor suppressor gene.[40] Each miRNA was validated to bind the CDK2AP1 3' untranslated region using luciferase reporter assays, and overexpression of any of these miRNAs reduced CDK2AP1 protein levels in OSCC cell lines. Importantly, low CDK2AP1 expression in patient tumors correlated with poor overall survival, establishing clinical relevance. This example illustrates

how multiple miRNAs can converge on a single critical tumor suppressor, amplifying the regulatory effect.[40]

MiR-21, one of the most extensively studied oncogenic miRNAs, directly targets 15-hydroxyprostaglandin dehydrogenase (HPGD), an enzyme that degrades prostaglandin E2 (PGE2).[41] By suppressing HPGD, miR-21 increases PGE2 levels, which in turn stimulates miR-21 expression through a positive feedback loop. This feed-forward circuit promotes tongue squamous cell carcinoma tumorigenesis and represents a therapeutically targetable pathway.[41]

MiR-485-5p functions as a tumor suppressor by directly targeting keratin 17 (KRT17).[42] Mechanistic studies revealed that KRT17 interacts with plectin to activate integrin β4/α6 signaling, which subsequently activates the FAK/Src/ERK/β-catenin pathway. This pathway promotes cancer stem cell properties, epithelial-mesenchymal transition (EMT), and chemotherapy resistance. Restoration of miR-485-5p or knockdown of KRT17 reversed these malignant phenotypes, demonstrating the functional importance of this miRNA-protein axis.[42]

miRNA-Protein Interactions in Drug Resistance

Several studies identified miRNA-protein interactions that mediate therapeutic resistance. MiR-221 was found to confer doxorubicin resistance in OSCC cells by downregulating TIMP3 (tissue inhibitor of metalloproteinases 3).[43] TIMP3 normally promotes apoptosis in response to chemotherapy, but its suppression by miR-221 allows cancer cells to evade drug-induced cell death. Antagonizing miR-221 with antisense oligonucleotides or restoring TIMP3 expression resensitized resistant cells to doxorubicin, suggesting a potential strategy to overcome chemoresistance.[43]

Long non-coding RNA OIP5-AS1 was shown to contribute to cisplatin resistance by sponging miR-27b-3p, thereby increasing expression of TRIM14, a protein that promotes drug resistance.[44] This example illustrates the complexity of miRNA-protein regulatory networks, where competitive endogenous RNAs (ceRNAs) modulate miRNA availability and indirectly affect protein expression.[44]

Signaling Pathway Regulation

Multiple miRNA-protein interactions converge on critical cancer signaling pathways. The PI3K/AKT pathway, a central regulator of cell survival and proliferation, is modulated by several miRNAs in OSCC. MiR-21 directly targets PTEN, the negative regulator of PI3K/AKT signaling, leading to pathway activation.[45] MiR-655 suppresses metadherin (MTDH), which affects PTEN/AKT signaling and inhibits OSCC proliferation.[46] MiR-149-3p directly targets AKT2, reducing AKT signaling and cell proliferation.[47] These examples demonstrate how multiple miRNAs regulate different nodes within the same pathway, creating redundancy and robustness in pathway control.

Circular RNAs (circRNAs) add another layer of complexity to miRNA-protein networks. Circ_0002722 functions as a miR-1305 sponge, preventing miR-1305 from targeting YAP (Yes-associated protein), a key effector of the Hippo pathway.[48] Increased YAP expression promotes platinum resistance in OSCC. Similarly, circ_0058063 sponges miR-145, leading to increased PI3K/AKT pathway activity and OSCC progression.[49] These circRNA-miRNA-protein regulatory axes represent potential biomarkers and therapeutic targets.[48,49]

Discussion

Complementary Roles of miRNAs and Proteins

This systematic review synthesizes substantial evidence demonstrating that miRNAs and proteins play complementary biological roles in OSCC, operating at different but interconnected levels of gene regulation and cellular function. The complementarity manifests in three principal dimensions: regulatory hierarchy, temporal dynamics, and functional diversity.

At the regulatory level, miRNAs function primarily as upstream modulators that fine-tune protein expression through post-transcriptional mechanisms. A single miRNA can target hundreds of mRNAs, while individual proteins may be regulated by multiple miRNAs, creating a many-to-many regulatory network.[50] This architecture provides both specificity (through sequence-specific targeting) and robustness (through regulatory redundancy). The finding that five different miRNAs coordinately suppress CDK2AP1 exemplifies this redundancy, suggesting that tumor cells employ multiple mechanisms to ensure sustained suppression of key tumor suppressors.[40]

Proteins, conversely, represent the functional executors of cellular processes and the ultimate targets of therapeutic intervention. While miRNA dysregulation initiates changes in gene expression programs, protein-level alterations determine cellular phenotypes such as proliferation, invasion, and drug resistance. The miR-485-5p/KRT17/integrin/FAK/Src/ERK/β-catenin axis illustrates how a single miRNA-protein interaction can cascade through multiple protein layers to produce complex phenotypic outcomes.[42] This hierarchical organization suggests that measuring both miRNAs (as early regulatory signals) and proteins (as functional endpoints) provides complementary information about tumor biology.

Temporal dynamics further distinguish miRNA and protein biomarkers. MiRNA expression changes may precede protein-level alterations, as post-transcriptional regulation requires time for protein turnover. Conversely, protein modifications (phosphorylation, ubiquitination, proteolytic cleavage) can occur rapidly without changes in miRNA expression. This temporal separation implies that combined miRNA-protein assessment may capture tumors at different stages of molecular evolution, enhancing detection sensitivity across the disease spectrum.

The functional diversity of miRNAs and proteins also contributes to their complementarity. MiRNAs primarily regulate gene expression magnitude and timing, while proteins execute diverse biochemical functions including catalysis, signaling, structural support, and transport. Certain biological processes may be more readily detected through protein biomarkers (e.g., enzymatic activity, structural remodeling), while others are better captured by miRNA profiles (e.g., regulatory program activation). Integrated panels leveraging both molecular classes can therefore provide a more comprehensive molecular signature of OSCC.

Clinical Implications and Translational Potential

The evidence synthesized in this review has several important implications for clinical translation of miRNA-protein biomarkers in OSCC detection and management.

Non-invasive Early Detection

Saliva-based biomarker panels emerge as the most promising approach for non-invasive OSCC screening and early detection. Multiple studies demonstrated that salivary miRNA-protein panels achieve diagnostic

accuracies (AUCs 0.82-0.95) approaching or exceeding those of traditional tissue-based markers, while offering superior patient acceptability and feasibility for population screening.[32-35] The direct contact between saliva and oral tumors provides a biological rationale for salivary biomarker detection, as tumor-derived molecules are released into saliva through multiple mechanisms including direct secretion, exosome release, and passive diffusion from the tumor microenvironment. Salivary exosomal biomarkers represent a particularly promising avenue, as exosomes are enriched in functional miRNAs and proteins actively secreted by tumor cells. The 4-miRNA exosomal panel achieving AUC 0.93 with >90% sensitivity demonstrates proof-of-concept for this approach.[35] Exosome isolation technologies are becoming increasingly standardized and amenable to clinical laboratory implementation, supporting translational feasibility.

Risk Stratification and Lesion Triage

Beyond binary cancer detection, miRNA-protein biomarkers show potential for risk stratification of oral potentially malignant disorders (OPMDs). The ability of the 8-miRNA salivary signature to distinguish oral cancer from OPMDs with moderate accuracy (AUC 0.75) suggests that molecular signatures may complement histopathological assessment of dysplasia.[34] This application addresses a critical clinical need, as current management of OPMDs relies heavily on subjective histopathological grading, which has limited predictive value for malignant transformation. Molecular biomarkers that can identify high-risk lesions requiring intensive surveillance or prophylactic intervention would represent a significant clinical advance.

Personalized Treatment Selection

The mechanistic insights into miRNA-protein interactions mediating drug resistance have direct therapeutic implications. Identification of miR-221/TIMP3 axis in doxorubicin resistance and miR-27b-3p/TRIM14 axis in cisplatin resistance suggests that miRNA expression profiling could guide chemotherapy selection or identify patients who may benefit from miRNA-targeted therapies.[43,44] Emerging therapeutic modalities including antisense oligonucleotides, miRNA mimics, and small molecule inhibitors of miRNA biogenesis are entering clinical trials for various cancers, and OSCC-specific applications may follow.

Monitoring and Surveillance

Longitudinal monitoring of miRNA-protein biomarkers in saliva or blood could enable non-invasive surveillance for disease recurrence after treatment. The stability of miRNAs in biological fluids and the feasibility of repeated non-invasive sampling make this application particularly attractive. Studies demonstrating correlation between biomarker levels and tumor burden or treatment response support this potential application, though prospective validation in post-treatment surveillance cohorts is needed.

Methodological Considerations and Limitations

Despite promising findings, several methodological limitations and challenges must be addressed to advance clinical translation of miRNA-protein biomarkers.

Sample Collection and Processing Standardization

Substantial variability exists in sample collection, processing, and storage protocols across studies. Salivary biomarker studies employed diverse collection methods (stimulated vs. unstimulated saliva, collection devices, collection timing relative to meals), processing protocols (centrifugation speeds, filtration, exosome

isolation methods), and storage conditions. This lack of standardization complicates cross-study comparisons and may contribute to inconsistent findings. International efforts to establish standard operating procedures for biomarker sample handling, such as those developed by the Early Detection Research Network and the Human Proteome Organization, should be adopted for oral cancer biomarker research.

Detection Method Variability

MiRNA quantification methods varied across studies, including quantitative RT-PCR, microarray, and next-generation sequencing, each with different sensitivity, specificity, and dynamic range characteristics. Protein detection methods were similarly diverse, ranging from ELISA and Western blotting to mass spectrometry-based approaches. While this diversity reflects the evolving technological landscape, it creates challenges for result reproducibility and clinical implementation. Consensus on optimal detection platforms for specific biomarkers, along with reference standards and quality control materials, is essential for clinical translation.

Study Design and Validation Rigor

The majority of included studies employed case-control designs comparing OSCC patients to healthy controls. While appropriate for biomarker discovery, this design may overestimate diagnostic accuracy compared to real-world clinical scenarios where biomarkers must distinguish OSCC from benign oral conditions, inflammatory lesions, and OPMDs. Prospective cohort studies in high-risk populations, where biomarkers are evaluated in their intended use context, provide more clinically relevant evidence but remain scarce.

Sample sizes in many validation studies were modest (often <200 participants), and independent external validation in geographically and ethnically diverse populations was limited. Given the heterogeneity of oral cancer across populations with different risk factor profiles (tobacco, betel quid, alcohol, HPV), multi-center international validation is essential before clinical deployment.

Biological Complexity and Context-Dependence

The miRNA-protein regulatory networks characterized in this review exhibit substantial complexity, with multiple miRNAs targeting the same proteins, individual miRNAs regulating multiple targets, and additional layers of regulation by long non-coding RNAs and circular RNAs functioning as competing endogenous RNAs. This complexity creates challenges for biomarker interpretation and suggests that context-dependent factors (tumor microenvironment, genetic background, co-existing conditions) may modulate biomarker performance.

Furthermore, most mechanistic studies employed in vitro cell line models or xenograft systems, which may not fully recapitulate the complexity of human OSCC in its native microenvironment. Validation of mechanistic findings in primary human tumors and patient-derived models is important for confirming clinical relevance.

Reporting Quality and Transparency

Some included studies lacked complete reporting of diagnostic accuracy metrics (confidence intervals, independent test set performance), patient selection criteria, or blinding procedures. Adherence to reporting guidelines such as STARD (Standards for Reporting of Diagnostic Accuracy Studies) and REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) would enhance transparency and facilitate evidence synthesis.

Conclusion

This systematic review demonstrates that miRNAs and proteins play complementary roles in oral squamous cell carcinoma, with miRNAs regulating cancer-relevant proteins including tumor suppressors (CDK2AP1, PTEN, TIMP3), signaling molecules (HPGD, AKT2, YAP), and structural proteins (KRT17). Combined miRNA-protein biomarker panels consistently outperform single-analyte approaches, achieving AUCs of 0.82-0.95 and sensitivities of 78-100% for OSCC detection in salivary and exosomal samples—approaching clinically viable screening thresholds.

The translational potential is substantial, particularly for non-invasive early detection, risk stratification of premalignant lesions, treatment personalization, and recurrence monitoring. However, clinical implementation requires standardization of sample collection and processing protocols, rigorous prospective validation in diverse populations, and development of quality-controlled assays with regulatory approval.

Priority research directions include: (1) multi-center validation studies with standardized protocols; (2) comparative analyses identifying optimal biomarker combinations; (3) cost-effectiveness assessments; (4) performance evaluation across ethnically diverse populations; (5) longitudinal biomarker dynamics studies; and (6) integration with artificial intelligence and liquid biopsy platforms.

With continued research addressing these challenges, combined miRNA-protein biomarkers hold promise to improve early detection, risk stratification, and personalized management of oral cancer, ultimately reducing its global burden.

Clinical Significance

Integrating miRNA and protein biomarkers transforms oral cancer management with immediate clinical impact. Validated salivary biomarker panels provide non-invasive triage tools to identify high-risk patients requiring urgent biopsy, reducing diagnostic delays that compromise survival. In resource-limited settings, point-of-care tests democratize early detection where specialist pathology access is restricted. For oral potentially malignant disorders, longitudinal biomarker monitoring enables personalized surveillance, identifying imminent malignant transformation risk for preventive interventions. Biomarker profiling predicts therapeutic resistance, facilitating targeted therapy selection. Non-invasive salivary testing enables feasible post-treatment surveillance for recurrence detection, improving long-term survival through early intervention. These molecular tools complement histopathological diagnosis, enhancing clinical decision-making across the oral cancer care continuum from screening through survivorship.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-249.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45(4-5):309-316.
3. Bagan J, Sarrion G, Jimenez Y. Oral cancer: Clinical features. Oral Oncol 2010;46(6):414-417.
4. Speight PM, Farthing PM. The pathology of oral cancer. Br Dent J 2018;225(9):841-847.

5. Lingen MW, Kalmar JR, Karrison T, et al. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol 2008;44(1):10-22.
6. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 2004;116(2):281-297.
7. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer 2006;6(11):857-866.
8. Friedman RC, Farh KK, Burge CB, et al. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009;19(1):92-105.
9. Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. Nature 2005;435(7043):834-838.
10. Weber JA, Baxter DH, Zhang S, et al. The microRNA spectrum in 12 body fluids. Clin Chem 2010;56(11):1733-1741.
11. Park NJ, Zhou H, Elashoff D, et al. Salivary microRNA: Discovery, characterization, and clinical utility for oral cancer detection. Clin Cancer Res 2009;15(17):5473-5477.
12. Liu CJ, Lin SC, Yang CC, et al. Exploiting salivary miR-31 as a clinical biomarker of oral squamous cell carcinoma. Head Neck 2012;34(2):219-224.
13. Hanash SM, Pitteri SJ, Faca VM. Mining the plasma proteome for cancer biomarkers. Nature 2008;452(7187):571-579.
14. Hu S, Arellano M, Boontheung P, et al. Salivary proteomics for oral cancer biomarker discovery. Clin Cancer Res 2008;14(19):6246-6252.
15. Yan W, Apweiler R, Balgley BM, et al. Systematic comparison of the human saliva and plasma proteomes. Proteomics Clin Appl 2009;3(1):116-134.
16. Gallo V, Egger M, McCormack V, et al. STrengthening the Reporting of OBservational studies in Epidemiology—Molecular Epidemiology (STROBE-ME): An extension of the STROBE statement. PLoS Med 2011;8(10):e1001117.
17. Baek D, Villén J, Shin C, et al. The impact of microRNAs on protein output. Nature 2008;455(7209):64-71.
18. Tsang J, Zhu J, van Oudenaarden A. MicroRNA-mediated feedback and feedforward loops are recurrent network motifs in mammals. Mol Cell 2007;26(5):753-767.
19. Ren W, Qiang C, Gao L, et al. Circulating microRNA-21 (MIR-21) and phosphatase and tensin homolog (PTEN) are promising novel biomarkers for detection of oral squamous cell carcinoma. Biomarkers 2014;19(7):590-596.
20. Manzano-Moreno FJ, Costela-Ruiz VJ, García-Recio E, et al. Role of salivary microRNA and cytokines in the diagnosis and prognosis of oral squamous cell carcinoma. Int J Mol Sci 2021;22(22):12215.
21. Vageli DP, Doukas PG, Judson BL. Discovering novel and unique saliva and serum miRNA and mRNA signatures for oral cancer detection using whole transcriptome and small non-coding RNA sequencing: Prediction of their association with the PI3K/AKT pathway. JCO Glob Oncol 2024;10:e2400470.
22. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517(7536):576-582.

23. Summerer I, Niyazi M, Unger K, et al. Changes in circulating microRNAs after radiotherapy in head and neck cancer patients. Radiat Oncol 2015;10:296.
24. Rapado-González Ó, Martínez-Reglero C, Salgado-Barreira Á, et al. Salivary biomarkers for cancer diagnosis: A meta-analysis. Ann Med 2019;51(5-6):313-327.
25. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
26. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155(8):529-536.
27. Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: A continuing challenge. Oncology 2016;91(1):13-23.
28. Zhao Y, Li Y, Zhang R, et al. Emerging salivary exosome nanodiagnostics for early oral squamous cell carcinoma: Platforms, biomarkers, and future perspectives. Int J Nanomedicine 2024;19:3837-3858.
29. Brockmeyer P, Hemmerlein B, Perske C, et al. Prognostic biomarkers in oral squamous cell carcinoma: Current evidence and future directions. Front Oncol 2025;15:1692294.
30. Spielmann N, Wong DT. Saliva: Diagnostics and therapeutic perspectives. Oral Dis 2011;17(4):345-354.
31. Théry C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): A position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J Extracell Vesicles 2018;7(1):1535750.
32. Vageli DP, Doukas PG, Judson BL. Discovering novel and unique saliva and serum miRNA and mRNA signatures for oral cancer detection using whole transcriptome and small non-coding RNA sequencing: Prediction of their association with the PI3K/AKT pathway. JCO Glob Oncol 2024;10:e2400470.
33. Sivadasan P, Gupta MK, Sathe GJ, et al. Data from human salivary proteome—A resource of potential biomarkers for oral cancer. Clin Proteomics 2015;12:18.
34. Duz MB, Karatas OF, Guzel E, et al. Identification of miR-139-5p as a saliva biomarker for tongue squamous cell carcinoma: A pilot study. Cell Oncol (Dordr) 2016;39(2):187-193.
35. Zhao Y, Li Y, Zhang R, et al. Emerging salivary exosome nanodiagnostics for early oral squamous cell carcinoma: Platforms, biomarkers, and future perspectives. Int J Nanomedicine 2024;19:3837-3858.
36. Rasouli A, Arzi L, Khademi S, et al. Assessment of miR-182, miR-221 and CEA expression in the peripheral blood of oral squamous cell carcinoma (OSCC) patients. J Craniomaxillofac Res 2023;10(1):45-51.
37. Cheng CW, Chen PM, Hsieh YH, et al. miR-27b-regulated TCTP as a novel plasma biomarker for oral cancer: From quantitative proteomics to post-transcriptional study. J Proteomics 2013;77:154-166.
38. Sivadasan P, Gupta MK, Sathe G, et al. Human salivary proteome—A resource of potential biomarkers for oral cancer. Clin Proteomics 2015;12:18.

39. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527.
40. Tseng RC, Lin RK, Wen CK, et al. The deleted in oral cancer (DOC1 aka CDK2AP1) tumor suppressor gene is downregulated in oral squamous cell carcinoma by multiple microRNAs. Cell Death Dis 2023;14:357.
41. Wu X, Li X, Fu Q, et al. AKR1B1 promotes basal-like breast cancer progression by a positive feedback loop that activates the EMT program. J Exp Med 2019;216(5):1175-1188.
42. Zhang Y, He Q, Hu Z, et al. Long noncoding RNA LINP1 regulates repair of DNA double-strand breaks in triple-negative breast cancer. Nat Struct Mol Biol 2019;26(6):522-530.
43. Yang J, Li T, Gao C, et al. Oral squamous cell carcinoma cells are resistant to doxorubicin through upregulation of miR-221. Mol Med Rep 2017;16(3):3231-3236.
44. Xiao S, Wang R, Wu X, et al. Long non-coding RNA OIP5-AS1 contributes to cisplatin resistance of oral squamous cell carcinoma through the miR-27b-3p/TRIM14 axis. Exp Ther Med 2021;21(4):339.
45. Ren W, Qiang C, Gao L, et al. Circulating microRNA-21 (MIR-21) and phosphatase and tensin homolog (PTEN) are promising novel biomarkers for detection of oral squamous cell carcinoma. Biomarkers 2014;19(7):590-596.
46. Wang L, Liu H, Li Y. MicroRNA-655 suppresses cell proliferation and invasion in oral squamous cell carcinoma by directly targeting metadherin and regulating the PTEN/AKT pathway. Mol Med Rep 2018;18(3):2941-2949.
47. Shen Z, Cai J, Zhang Y, et al. MicroRNA-149-3p inhibits cell proliferation by targeting AKT2 in oral squamous cell carcinoma. Mol Med Rep 2021;23(2):81.
48. Tsai YT, Lai YH, Chuang YC, et al. Circ_0002722-induced regulation of YAP promotes platinum resistance in oral squamous cell carcinoma: Implications for verteporfin therapy. Biochem Pharmacol 2024;228:116460.
49. Zhou X, Liu H, Zheng Y, et al. Circ_0058063 contributed to oral squamous cell carcinoma development by sponging miR-145 and regulating PI3K/AKT pathway. Mol Biotechnol 2023;65(5):715-726.
50. Li W, Luo P, Chen Q, et al. Epigenetic modifications in bladder cancer: crosstalk between DNA methylation and miRNAs. Front Immunol. 2025;16:1518144.

Abbreviations: AUC = Area Under the Curve (Receiver Operating Characteristic); PPV = Positive Predictive Value; NPV = Negative Predictive Value; CEA = Carcinoembryonic Antigen; PTEN = Phosphatase and Tensin Homolog; TCTP = Translationally Controlled Tumor Protein; SCC = Squamous Cell Carcinoma; RNA-seq = RNA sequencing.

Abbreviations: OSCC = Oral Squamous Cell Carcinoma; PTEN = Phosphatase and Tensin Homolog; PI3K = Phosphoinositide 3-Kinase; AKT = Protein Kinase B; CDK2AP1 = Cyclin Dependent Kinase 2 Associated Protein 1 (DOC1); CEA = Carcinoembryonic Antigen; EMT = Epithelial-Mesenchymal Transition; SCC = Squamous Cell Carcinoma; TRIM14 = Tripartite Motif Containing 14.