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Altered miRNA Profiles in Oral Squamous Cell Carcinoma Patients Relative to Healthy Controls: A Systematic Review

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) remains a major cause of cancer morbidity and mortality, largely due to late-stage presentation and early metastatic potential. MicroRNAs (miRNAs) regulate oncogenic and tumor suppressive pathways and have emerged as promising diagnostic and prognostic biomarkers measurable in tissue and body fluids. Objective: To systematically identify miRNAs differentially expressed in OSCC patients compared with healthy controls across tissue, plasma, and saliva specimens. Methods: A PRISMA-guided systematic review was conducted using Embase, PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar, with ProQuest used to search grey literature. Eligible studies included human OSCC case–control designs reporting differential miRNA expression between OSCC cases and healthy controls using tissue, plasma, or saliva samples. Two reviewers performed study selection and data extraction independently, with methodological quality assessed using the Newcastle–Ottawa Scale. Findings were synthesized narratively due to heterogeneity in specimen types and miRNA targets. Results: Six case–control studies were included. In saliva, hsa-miR-30c-5p was downregulated, while hsa-miR-423-5p, hsa-miR-106b-5p, and hsa-miR-193b-3p were upregulated in OSCC. In plasma, hsa-miR-31 was upregulated. In tissue, downregulation of hsa-miR-204, hsa-miR-144, and hsa-miR-375 and upregulation of hsa-miR-196a, hsa-miR-21, and hsa-miR-155 were reported. Most studies were high quality. Conclusion: OSCC is associated with reproducible miRNA dysregulation across multiple biological matrices, supporting miRNAs as candidate biomarkers; however, evidence remains limited and requires standardized validation, including diagnostic accuracy assessment and external replication.

Keywords
oral squamous cell carcinoma, microRNA, saliva, plasma, tissue, qRT-PCR, biomarker, differential expression.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents the most common malignancy of the oral cavity and remains a major global health concern due to its aggressive biological behavior, tendency for early locoregional and distant metastasis, and substantial risk of recurrence even following definitive therapy (1). Despite advances in surgical reconstruction, radiotherapy planning, and systemic treatments, survival outcomes have improved only modestly, largely because many patients present at advanced stages when curative intervention becomes less effective (2). Early detection therefore remains a central priority in OSCC control strategies, and there is continued interest in molecular biomarkers that can improve risk stratification, support earlier diagnosis, and potentially guide prognostication beyond conventional clinicopathologic parameters (2).

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally and play critical roles in cancer-related pathways involving proliferation, apoptosis, angiogenesis, epithelial–mesenchymal transition, invasion, and metastatic dissemination (3). Dysregulation of miRNA networks is increasingly recognized as a hallmark of carcinogenesis, including OSCC, where specific miRNAs may exert oncogenic activity through suppression of tumor suppressor genes or, conversely, act as tumor suppressors by inhibiting oncogenic signaling (4). Importantly, miRNAs can be detected in multiple biological matrices relevant to OSCC, including tissue, plasma, and saliva, and their stability in extracellular environments makes them attractive candidates for minimally invasive biomarker development (4).

The molecular heterogeneity of OSCC is well established, and profiling studies have identified numerous miRNAs with altered expression in malignant tissue compared with non-malignant controls (5). Among these, miR-31 has been repeatedly described as a potential diagnostic signal, with evidence suggesting upregulation across tissue and circulating specimens (6). In contrast, miR-375 has been reported as consistently downregulated and linked to clinically relevant outcomes, including disease aggressiveness and treatment responsiveness (7). Such differential expression patterns have also been explored as tools for distinguishing malignant from non-malignant tissue and for enhancing prognostic

assessment (8). Additionally, miR-21 has emerged as a prominent oncogenic miRNA with reported overexpression in OSCC, including saliva and tissue, and has been associated with adverse pathological and survival outcomes (9). Other miRNAs implicated across OSCC datasets include members of the miR-196 family and miR-203 as frequently upregulated candidates, while let-7 family members and miR-16 are often reported as downregulated, reflecting disruption in pathways relevant to tumor progression and cellular differentiation (10). Salivary miRNA signatures have gained increasing attention because they offer a non-invasive route for detection and longitudinal monitoring, with several miRNAs reported as dysregulated in OSCC compared with controls (11).

Although multiple primary studies have reported differential expression of miRNAs in OSCC, the evidence remains fragmented across specimen types, analytical platforms, and study populations, and there is variation in the specific miRNAs reported as clinically useful (4). Prior reviews have primarily emphasized salivary miRNAs, single-miRNA candidates, or broader head and neck cancers rather than focusing specifically on OSCC and directly comparing expression patterns between confirmed OSCC cases and healthy controls across tissue, plasma, and saliva (4,9). Furthermore, differences in specimen handling, assay normalization, and study design can affect miRNA expression results and limit reproducibility and translation into clinically implementable testing strategies (4). A systematic synthesis centered on human OSCC case–control evidence, with explicit separation by biological matrix and measurement approach, may clarify which miRNAs demonstrate the most consistent differential expression and are therefore most plausible candidates for future validation.

The objective of this systematic review was to identify miRNAs differentially expressed in patients with oral squamous cell carcinoma compared with healthy controls, across tissue, plasma, and saliva specimens, and to summarize the direction of dysregulation and the methodological quality of the supporting evidence.

MATERIALS AND METHODS

This systematic review was conducted in accordance with established systematic review methodology and was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure transparent identification, selection, appraisal, and synthesis of evidence. The review was designed to summarize human case–control evidence evaluating differential miRNA expression in OSCC compared with healthy controls across relevant biological specimens. Given the expected heterogeneity in specimen types, analytical platforms, and reporting approaches, a narrative synthesis approach was used rather than quantitative pooling, and findings were reported by specimen category.

A comprehensive literature search was conducted using Embase, MEDLINE/PubMed, Web of Science, Scopus, and Google Scholar to identify eligible peer-reviewed studies. To capture grey literature and minimize publication bias, ProQuest was additionally searched. The search strategy combined controlled vocabulary terms (e.g., MeSH and Emtree where applicable) with free-text keywords related to OSCC and miRNA expression, including terms reflecting differential expression and specimen sources. Core concepts included oral squamous cell carcinoma, oral cancer, microRNA/miRNA, expression profiling, upregulation, downregulation, tissue, plasma, serum, saliva, and quantitative reverse transcription polymerase chain reaction. Boolean operators (“AND,” “OR”) were used to combine search blocks, and database-specific syntax was adapted accordingly. No restrictions were applied based on publication year, language, geography, ethnicity, or demographic characteristics to maximize evidence capture. In addition to electronic searching, reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies missed through database searching.

Eligibility criteria were defined a priori. Studies were eligible if they included patients with a confirmed diagnosis of oral squamous cell carcinoma and a healthy control group, and if they evaluated differential expression of one or more miRNAs in OSCC cases compared with controls. Studies were required to analyze miRNA expression using tissue, plasma, or saliva specimens, and to report the direction of dysregulation (upregulated or downregulated) in cases versus controls. Animal studies were excluded, as were studies focusing on cancers other than OSCC, and studies centered on oral potentially malignant disorders or leukoplakia without a distinct OSCC case–control comparison. Studies without healthy controls were excluded. Where multiple publications appeared to derive from the same cohort, the most comprehensive report was prioritized.

All records retrieved from the search were screened using a two-stage process. Titles and abstracts were screened first to remove clearly irrelevant studies, followed by full-text screening of potentially eligible articles against the predefined criteria. Screening was conducted independently by two reviewers, and disagreements were resolved through discussion to achieve consensus. Reasons for exclusion at the full-text stage were documented systematically and reported in the excluded studies summary and PRISMA flow diagram.

Data extraction was conducted independently by two reviewers using a standardized extraction framework to ensure consistency and completeness. Extracted variables included author and publication year, study design, sample type (tissue, plasma, saliva), number of OSCC cases and controls, miRNA(s) evaluated, assay platform used for miRNA quantification (e.g., qRT-PCR, microarray with qRT-PCR validation), and the reported direction of differential expression in OSCC compared with controls. Any discrepancies in extraction were resolved by consensus discussion. Because this review synthesized published data, study authors were not contacted for additional information.

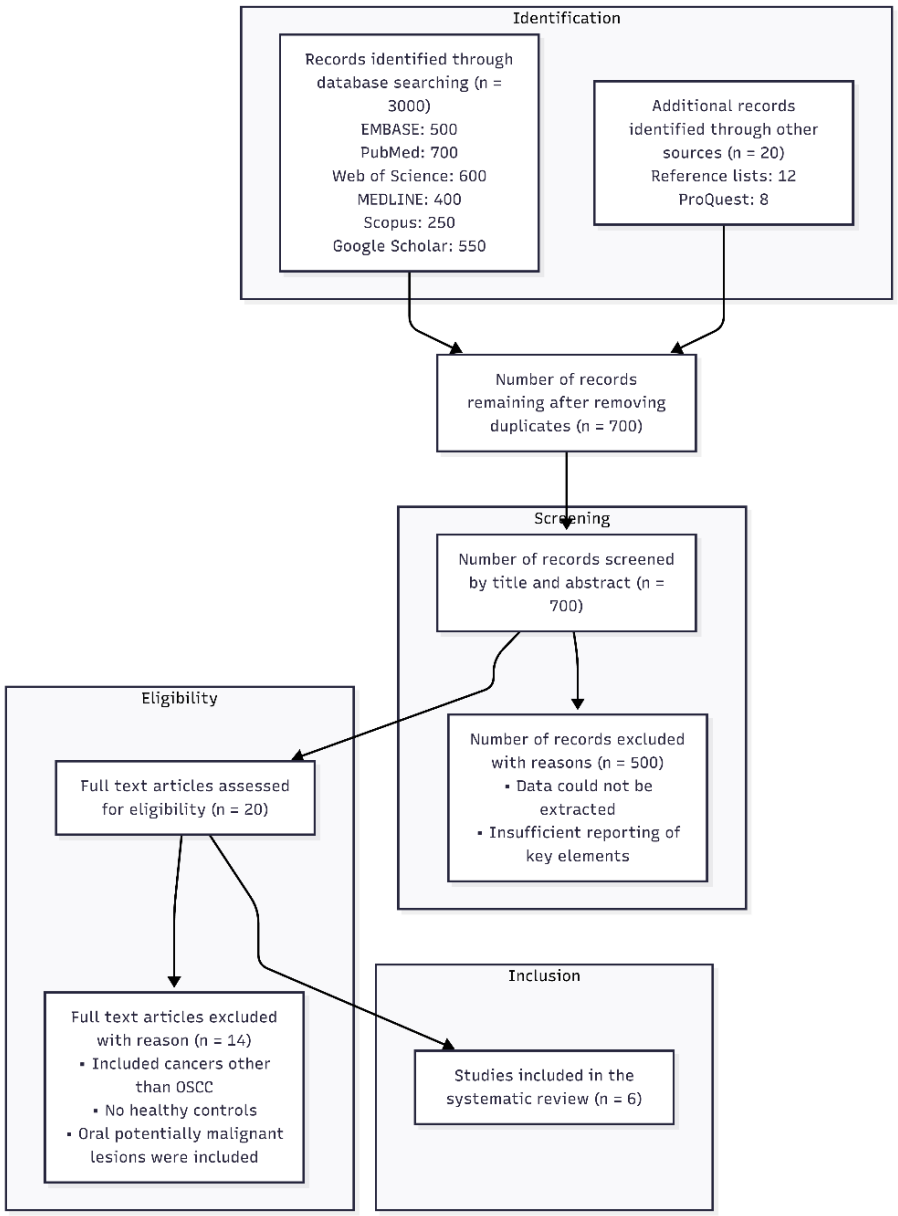

Figure 1 PRISMA Flowchart

Methodological quality and risk of bias of included case–control studies were assessed using the Newcastle–Ottawa Scale (NOS), which evaluates selection of study groups, comparability of cases and controls, and ascertainment of exposure. Scores were categorized as high/good quality (7–9), fair/moderate quality (5–6), and poor/low quality (<5) to support interpretation of the strength and reliability of evidence. Quality assessments were performed independently by two reviewers, and differences were resolved by discussion.

Given heterogeneity in specimen sources, miRNA targets, and reporting metrics, a formal meta-analysis was not performed. Instead, findings were synthesized narratively and organized by biological matrix, with emphasis on the direction of miRNA dysregulation (upregulation or downregulation) in OSCC relative to healthy controls and the methodological quality of supporting studies. Ethical approval was not required because the review involved secondary analysis of previously published data.

RESULTS

Six eligible case–control studies were included in this systematic review, collectively evaluating differential miRNA expression in OSCC patients compared with healthy controls across saliva, plasma, and tissue specimens (Table 1). Two studies assessed salivary miRNAs, one study assessed plasma miRNA expression, and three studies evaluated tumor tissue specimens (Table 2).

The predominant analytical method was qRT-PCR, with one study employing genome-wide microarray profiling followed by qRT-PCR validation (Table 2). Due to heterogeneity in specimen matrices and the limited overlap of specific miRNAs across studies, a meta-analysis was not performed, and findings were synthesized narratively by biological matrix (Table 4).

The included studies were predominantly high quality based on the Newcastle–Ottawa Scale, with five studies scoring 8–9, indicating high methodological rigor and low risk of bias within the constraints of observational case–control design (Table 3). One study was rated moderate quality (NOS score 7), reflecting minor limitations in domains related to control definition and/or comparability (Table 3).

Overall, the risk-of-bias profile supports reasonable confidence in the directionality of the reported miRNA dysregulation signals, while acknowledging that most candidates were reported by single studies and require replication.

Table 1. Evidence on differential miRNA expression in OSCC versus healthy controls

Characteristic	Summary
Review focus	Differential miRNA expression in OSCC cases versus healthy controls
Included studies (n)	6
Study design	All case–control studies
Sample matrices assessed	Saliva (n = 2 studies), Plasma (n = 1), Tissue (n = 3)
miRNA analytical platforms	qRT-PCR alone (n = 5), microarray with qRT-PCR validation (n = 1)
Evidence synthesis	Narrative synthesis (meta-analysis not performed due to heterogeneity in specimen type and miRNA targets)
Core finding	Multiple miRNAs showed consistent direction of dysregulation within specific specimen types; most miRNAs were reported in single studies per matrix

Table 2. Characteristics of studies evaluating differential miRNA expression in OSCC versus healthy controls

Study (Year)	Design	Sample type	Cases (n)	Controls (n)	miRNAs evaluated	Direction in OSCC	Expression platform
Mehterov et al. (2021) (12)	Case–control	Saliva	33	12	hsa-miR-30c-5p	Downregulated	qRT-PCR
Romani et al. (2021) (11)	Case–control	Saliva	89	58	hsa-miR-423-5p; hsa-miR-106b-5p; hsa-miR-193b-3p	Upregulated	Microarray + qRT-PCR
Caliaperoumal et al. (2022) (13)	Case–control	Plasma	25	25	hsa-miR-31	Upregulated	qRT-PCR
Rajan et al. (2021) (5)	Case–control	Tissue	144	36	hsa-miR-196a; hsa-miR-204; hsa-miR-144	miR-196a upregulated; miR-204 & miR-144 downregulated	qRT-PCR
Gombos et al. (2013) (14)	Case–control	Tissue	40	40	hsa-miR-21; hsa-miR-155	Upregulated	qRT-PCR
Narasimhan et al. (2023) (15)	Case–control	Tissue	22	22	hsa-miR-375	Downregulated	qRT-PCR

*NR: Not reported in the manuscript text provided. Abbreviations: miRNA, microRNA; OSCC, oral squamous cell carcinoma; qRT-PCR, quantitative reverse transcription polymerase chain reaction; NR, not reported.

Table 3. Newcastle–Ottawa Scale (NOS) quality assessment of included case–control studies

Study	NOS score (0–9)	Overall quality category	Key quality considerations (as per NOS domains)
Mehterov et al. (2021) (12)	7	Moderate	Minor limitations in control definition/comparability scoring
Caliaperoumal et al. (2022) (13)	8	High	Strong selection/exposure assessment; high comparability
Romani et al. (2021) (11)	9	High	High methodological rigor across domains
Rajan et al. (2021) (5)	9	High	High selection and comparability; robust ascertainment
Gombos et al. (2013) (14)	9	High	High rigor; balanced groups and clear exposure ascertainment
Narasimhan et al. (2023) (15)	8	High	Strong design and exposure ascertainment; comparability adequate

Table 4. Direction of miRNA dysregulation in OSCC relative to healthy controls, by biological matrix

Specimen type	Study (year)	miRNA(s)	Direction in OSCC vs controls
Saliva	Mehterov et al. (2021) (12)	hsa-miR-30c-5p	Downregulated
Saliva	Romani et al. (2021) (11)	hsa-miR-423-5p	Upregulated
Saliva	Romani et al. (2021) (11)	hsa-miR-106b-5p	Upregulated
Saliva	Romani et al. (2021) (11)	hsa-miR-193b-3p	Upregulated
Plasma	Caliaperoumal et al. (2022) (13)	hsa-miR-31	Upregulated
Tissue	Rajan et al. (2021) (5)	hsa-miR-196a	Upregulated
Tissue	Rajan et al. (2021) (5)	hsa-miR-204	Downregulated
Tissue	Rajan et al. (2021) (5)	hsa-miR-144	Downregulated
Tissue	Gombos et al. (2013) (14)	hsa-miR-21	Upregulated
Tissue	Gombos et al. (2013) (14)	hsa-miR-155	Upregulated
Tissue	Narasimhan et al. (2023) (15)	hsa-miR-375	Downregulated

Table 5. Consolidated miRNA signal map across specimen types (counts reflect number of included studies reporting the miRNA in that matrix)

miRNA	Saliva (studies)	Plasma (studies)	Tissue (studies)	Direction reported
hsa-miR-30c-5p	1	0	0	Downregulated
hsa-miR-423-5p	1	0	0	Upregulated
hsa-miR-106b-5p	1	0	0	Upregulated
hsa-miR-193b-3p	1	0	0	Upregulated
hsa-miR-31	0	1	0	Upregulated
hsa-miR-196a	0	0	1	Upregulated
hsa-miR-204	0	0	1	Downregulated
hsa-miR-144	0	0	1	Downregulated
hsa-miR-21	0	0	1	Upregulated
hsa-miR-155	0	0	1	Upregulated
hsa-miR-375	0	0	1	Downregulated

Across salivary studies, one study reported that hsa-miR-30c-5p was downregulated in OSCC cases compared with healthy controls, suggesting a potential tumor-suppressive biomarker signal within saliva (12). In contrast, a genome-wide salivary profiling study identified hsa-miR-423-5p,

hsa-miR-106b-5p, and hsa-miR-193b-3p as upregulated in OSCC patients relative to controls, indicating a distinct salivary miRNA signature associated with OSCC (11). These findings demonstrate that both upregulated and downregulated miRNA patterns can be detected non-invasively in saliva, although the evidence is currently limited to single-study reports for each candidate (Table 4 and Table 5).

In plasma, one case–control study reported upregulation of hsa-miR-31 in OSCC cases compared with healthy controls, supporting the potential utility of circulating miRNAs as minimally invasive biomarkers (13). However, as only one included plasma study was available, the strength of evidence remains preliminary and requires validation across independent cohorts using standardized pre-analytic and analytic approaches (Table 4 and Table 5). In tissue specimens, three studies identified multiple dysregulated miRNAs in OSCC relative to controls. One study reported upregulation of hsa-miR-196a alongside downregulation of hsa-miR-204 and hsa-miR-144, supporting the presence of both oncogenic and tumor-suppressive miRNA alterations within malignant tissue (5). Another study demonstrated upregulation of hsa-miR-21 and hsa-miR-155, two widely recognized oncogenic miRNAs implicated in cancer-related regulatory networks (14). A further study reported downregulation of hsa-miR-375 in OSCC tissue compared with controls, reinforcing the importance of tumor-suppressor miRNA depletion in OSCC biology (15). Collectively, tissue-based studies demonstrated consistent direction of dysregulation for each evaluated miRNA, although overlap across studies was limited (Table 4 and Table 5).

DISCUSSION

This systematic review synthesized human case–control evidence evaluating differential miRNA expression in oral squamous cell carcinoma (OSCC) compared with healthy controls across tissue, plasma, and saliva specimens. Across six included studies, several miRNAs demonstrated consistent directionality of dysregulation within specific biological matrices, including upregulated miRNAs in saliva (hsa-miR-423-5p, hsa-miR-106b-5p, hsa-miR-193b-3p) and downregulated salivary hsa-miR-30c-5p, upregulated plasma hsa-miR-31, and tissue-based upregulation of hsa-miR-196a, hsa-miR-21, and hsa-miR-155 alongside downregulation of hsa-miR-204, hsa-miR-144, and hsa-miR-375 (5,11–15). Collectively, these findings support the concept that OSCC is characterized by aberrant miRNA regulation that can be detected not only in tumor tissue but also through minimally invasive sampling, thereby reinforcing the broader premise that miRNAs represent plausible diagnostic and prognostic biomarker candidates (3,4).

The dysregulated miRNAs identified in this review align with established mechanistic frameworks implicating miRNAs in oncogenic and tumor suppressive pathways relevant to OSCC biology. miRNAs modulate key cellular processes such as proliferation, apoptosis, invasion, angiogenesis, and epithelial–mesenchymal transition, thereby influencing malignant transformation and metastatic competence (3,4). The identification of tissue upregulation of oncogenic candidates such as miR-21 and miR-155 is consistent with literature linking these miRNAs to tumor-promoting signaling and adverse clinical features in OSCC and related head and neck malignancies (9,14). Similarly, downregulation of tumor suppressive miRNAs such as miR-375 is repeatedly reported in OSCC and has been associated with aggressive disease biology and poorer outcomes, supporting its relevance as both a biological marker and a potential functional mediator of carcinogenesis (7,15,34). The tissue signal observed for miR-196a, together with depletion of miR-204 and miR-144, is also concordant with profiling studies suggesting that OSCC progression involves coordinated activation of oncogenic miRNA programs and suppression of differentiation- and apoptosis-associated regulatory pathways (5,10).

A key translational feature of the evidence base is the detection of miRNA dysregulation in saliva and plasma, which supports the feasibility of non-invasive biomarker strategies for OSCC screening and monitoring. Saliva is particularly appealing given proximity to the tumor microenvironment, ease of repeated sampling, and suitability for population-level implementation, which aligns with broader oral cancer screening priorities aimed at improving early detection in high-risk groups (2,4).

The included salivary studies support the existence of a diagnostic signature involving upregulated miR-423-5p, miR-106b-5p, and miR-193b-3p and downregulated miR-30c-5p, suggesting that OSCC may generate reproducible salivary miRNA alterations measurable using qRT-PCR or validated discovery platforms (11,12). Likewise, the plasma upregulation of miR-31 observed in this review is consistent with prior work indicating that circulating miR-31 has utility as a marker for oral cancer and may decrease following tumor resection, implying responsiveness to tumor burden (13,33). These findings collectively support the overarching direction of the field: miRNA panels may ultimately provide more robust diagnostic value than single biomarkers, particularly when integrated with clinicopathological risk markers or adjunctive screening modalities (2,6).

Despite the biological plausibility and consistency in directionality for the miRNAs reported in each included study, several limitations constrain the certainty and immediate clinical applicability of the evidence. First, the dataset was small (six studies), and most miRNAs were reported in single studies per specimen type, limiting replication and restricting inference about generalizability across settings and populations (5,11–15). Second, heterogeneity in pre-analytic handling (collection methods, storage conditions, extraction protocols), analytic workflows (normalization controls, qRT-PCR platforms, threshold definitions), and reporting practices can substantially influence measured miRNA expression and may explain variability across the broader literature (4). Third, case–control designs are vulnerable to selection bias and confounding, particularly when control populations are not matched on key determinants such as smoking, betel nut use, inflammation, periodontal disease, or metabolic comorbidity, all of which may influence miRNA profiles independent of OSCC status (4).

Fourth, although differential expression is necessary for biomarker candidacy, relatively few studies in this evidence base reported standardized diagnostic performance measures (e.g., AUC, sensitivity, specificity) or validated biomarker cutoffs, limiting translation into clinically actionable screening tests (11–13).

Finally, OSCC is heterogeneous with respect to anatomical subsites, tumor stage, and molecular phenotype; without consistent stratification, miRNA signals may represent composite averages rather than stage-specific or subtype-specific diagnostic markers (1,5).

The methodological strengths of this review include a broad database search, inclusion of multiple specimen types (tissue, plasma, saliva), and formal quality appraisal using the Newcastle–Ottawa Scale, which indicated generally high quality across included studies (11–15). However, the review is limited by the inability to perform quantitative synthesis because of heterogeneity in targets and specimen matrices and by incomplete harmonization across study reporting, which prevented robust comparisons of effect sizes.

These limitations underscore the need for future research prioritizing standardized laboratory workflows, harmonized reporting of normalization methods and effect measures, and validation in large, prospective, multi-center cohorts. Additionally, future work should focus on developing and validating multi-miRNA panels rather than single biomarkers, incorporating external validation, assessing diagnostic accuracy against clinically

meaningful reference standards, and evaluating implementation feasibility in screening pathways, especially in high-risk populations (2,4,9). Longitudinal designs evaluating pre-diagnostic and post-treatment trajectories may also clarify whether miRNAs function primarily as diagnostic discriminators, prognostic indicators, or dynamic markers of treatment response and recurrence (33,34).

CONCLUSION

This systematic review identified aberrant miRNA expression in OSCC compared with healthy controls across saliva, plasma, and tissue, including salivary upregulation of hsa-miR-423-5p, hsa-miR-106b-5p and hsa-miR-193b-3p with downregulation of hsa-miR-30c-5p, plasma upregulation of hsa-miR-31, and tissue upregulation of hsa-miR-196a, hsa-miR-21 and hsa-miR-155 alongside downregulation of hsa-miR-204, hsa-miR-144 and hsa-miR-375. While these signals support the promise of miRNAs as minimally invasive biomarkers and reflect plausible oncogenic and tumor suppressive mechanisms, the evidence is largely based on single-study findings per matrix and remains limited by methodological heterogeneity and incomplete diagnostic performance reporting. Future large-scale, standardized, multicenter, longitudinal studies should validate reproducible miRNA panels and establish clinically meaningful thresholds to enable translation into screening, risk stratification, and monitoring pathways for OSCC.

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