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Salivary Biomarkers in the Early Diagnosis of Oral Diseases

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ABSTRACT

Early diagnosis can reduce morbidity from oral squamous cell carcinoma (OSCC), prevent irreversible periodontal destruction, and target preventive care for dental caries. Saliva is an attractive diagnostic matrix because it is collected repeatedly and non-invasively and contains proteins, enzymes, cytokines, nucleic acids, metabolites, microorganisms, and extracellular vesicles (EVs) originating from glands, gingival crevicular fluid, mucosal transudate, blood, and local lesions. This review appraises salivary biomarkers for OSCC and oral potentially malignant disorders (OPMDs), caries, periodontal diseases, oral lichen planus (OLP), Sjögren syndrome, peri-implant disease, infections, and temporomandibular disorders. Across diseases, inflammatory proteins and matrix metalloproteinases show the most reproducible group differences. Messenger RNA, microRNA, methylation, broaden biological coverage but largely remain discovery-stage. For periodontitis, active MMP-8 is closest to chairside translation, but moderate discrimination precludes replacement of periodontal examination. Caries biomarkers currently support risk assessment rather than lesion diagnosis. Pre-analytical variation, confounding, inconsistent definitions, small samples, and poor reporting impede transportability. Salivary diagnostics are best positioned as adjunctive triage, risk, and monitoring tools.

Keywords: Saliva, Autoimmune diseases, Dental caries, Periodontal diseases, Salivary biomarkers

1.INTRODUCTION

Oral diseases cause pain, tooth loss, functional limitation, disfigurement, and substantial treatment burden. Their natural history makes timing consequential: dysplastic mucosal change may precede invasive OSCC, inflammatory periodontal lesions can progress before extensive radiographic bone loss is apparent, and caries is most reversible before cavitation. Routine diagnosis nevertheless remains dominated by visual-tactile examination, periodontal probing, radiography, culture or molecular microbiology, and—when malignancy is suspected—biopsy and histopathology. These are indispensable reference standards, but they may be operator dependent, episodic, invasive, insensitive to early molecular change, or unsuitable for frequent monitoring [25].

Whole saliva continuously samples oral surfaces. It contains products of epithelial turnover, leukocyte activity, microbial metabolism, gingival crevicular fluid (GCF), serum transudation, and glandular secretion. A useful diagnostic biomarker should discriminate clinically relevant states in the intended population, add value

beyond readily available information, be analytically robust, and improve decisions or outcomes. The field has expanded from targeted immunoassays to proteomic, transcriptomic, metabolomic, microbiomic, epigenomic, and EV platforms. Yet small convenience samples and comparisons of established disease with healthy controls remain common. This review therefore distinguishes biomarker discovery, analytical validation, clinical validation, and clinical utility [3,25].

2. Saliva as a Diagnostic Fluid

Saliva is approximately 99% water; electrolytes, mucins, immunoglobulins, antimicrobial peptides, enzymes, growth factors, lipids, hormones, nucleic acids, metabolites, cells, microorganisms, and vesicles comprise the remainder. Major and minor glands contribute gland-specific secretions, while whole saliva also contains desquamated epithelium, neutrophils, GCF, food debris, microbial products, and trace blood. Lesion-proximal molecules enter through shedding, exudation, apoptosis, necrosis, or vesicle release; systemic molecules may arrive by diffusion, transport, ultrafiltration, or GCF. This complexity captures local host–microbe interactions but also makes concentration dependent on flow and contamination [3,25].

Unstimulated whole saliva is simple and commonly preferred for oral-inflammatory and cancer studies. Stimulation yields larger volume but changes gland contribution, pH, bicarbonate, proteins, and concentration. Gland-specific saliva is mechanistically cleaner but technically difficult and less representative of the oral ecosystem. Choice must follow intended use. Protocols should report time, fasting, oral activity, device, duration, volume, flow, and recent dental procedures [25].

A defensible workflow generally includes prespecified avoidance of food, drink, smoking, oral hygiene, and vigorous exercise; mouth rinsing followed by rest; timed passive drool or standardized stimulation; immediate cooling; analyte-appropriate centrifugation and stabilization; aliquoting; and storage commonly at −80°C. Freeze–thaw cycles should be minimized. Cellular DNA, cell-free RNA, EVs, proteins, metabolites, and microbiota require different preservation. Normalization by volume, total protein, flow rate, spike-ins, or endogenous controls can yield different conclusions and must itself be validated [25].

Table 1. Major classes of salivary biomarkers and biological significance

Class	Examples	Meaning	Key limitation
Proteins/peptides	CD44, CYFRA21-1, defensins	Turnover, adhesion, innate defense	Proteolysis/flow
Enzymes	aMMP-8, MMP-9, LDH, amylase	Matrix degradation or injury	Activity ≠ abundance
Cytokines	IL-1β, IL-6, IL-8, TNF-α	Inflammatory signaling	Non-specific
DNA/RNA/miRNA	Methylation, cfDNA, mRNA, miR-21	Molecular change/regulation	Low abundance; instability
Metabolites/lipids	Lactate, polyamines, eicosanoids	Host–microbial phenotype	Diet/time effects
Microbial	Pathogens, dysbiosis signatures	Ecology and virulence	Carriage ≠ disease
EVs/exosomes	Protein/RNA/DNA cargo	Protected intercellular signals	Isolation not standardized

3. Classification of Salivary Biomarkers

Proteins and peptides are clinically accessible because immunoassay and lateral-flow formats are mature. Cytokeratin fragments and soluble CD44 reflect epithelial disruption; defensins, histatins, lactoferrin, calprotectin, and S100 proteins participate in antimicrobial defense.

Enzymes add functional information: lactate dehydrogenase (LDH) reflects cellular injury, while MMPs reflect extracellular-matrix remodeling. Active MMP-8 (aMMP-8) is more specific to ongoing collagenolysis than total abundance, although antibodies, activation states, and thresholds vary [5,7,17,25].

Interleukin (IL)-1β, IL-6, IL-8, and tumour necrosis factor alpha (TNF-α) plausibly mark inflammatory and malignant microenvironments but are not disease-specific. DNA and RNA approaches include mutation, copy-number change, promoter methylation, cell-free DNA fragmentation, messenger RNA, long non-coding RNA, microRNA (miRNA), and emerging PIWI-interacting RNA. They may encode mechanism but are vulnerable to degradation, leukocyte background, low tumour fraction, and pipeline choices [8,11,13].

Metabolomics measures downstream host–microbial phenotype but is sensitive to diet, fasting, hygiene, medication, and platform drift. Microbial markers quantify pathogens or community dysbiosis; ecological diseases are unlikely to be captured by one organism. EVs protect cargo and may enrich lesion signals, yet centrifugation, precipitation, size exclusion, and immunocapture yield non-equivalent populations. Lipid mediators, glycans, autoantibodies, oxidative products, volatile compounds, and cell phenotypes are additional emerging classes [3,24,25].

4. Salivary Biomarkers in Major Oral Diseases

4.1 Oral Cancer and Oral Potentially Malignant Disorders

Suspicious oral lesions still require biopsy. Salivary testing is best conceptualized as triage, adjunctive risk stratification, recurrence surveillance, or support where specialist examination is delayed. Meta-analyses repeatedly report elevated IL-6 and IL-8 in OSCC. IL-8 promotes neutrophil recruitment and angiogenesis; IL-6 activates JAK/STAT signaling. However, pooled estimates combine assays, thresholds, stages, and control groups, while periodontitis and tobacco exposure can raise the same cytokines [7,9].

MMP-9, LDH, chemerin, CD44, and CYFRA21-1 recur as protein candidates. MMP-9 reflects invasion; LDH reflects high turnover and injury; chemerin links inflammation and tumour biology; soluble CD44 reflects adhesion and shedding; CYFRA21-1 is released during epithelial injury. Panels involving IL-8, CYFRA21-1, and CD44 often outperform single markers. Yet comparisons of untreated OSCC with healthy volunteers do not establish early-stage screening performance. Advanced tumours, absence of benign inflammatory lesions, post-hoc cut-offs, and lack of blinded external validation produce optimism [4,5,7,12].

For OPMDs, the clinically important endpoint is dysplasia or malignant transformation, not lesion presence. Oxidative markers, LDH, MMPs, cytokines, miRNAs, methylation, and microbiome shifts show associations, but cross-sectional studies cannot prove prediction independent of grade, site, tobacco, or periodontal inflammation. Valid transformation biomarkers need longitudinal cohorts, time-to-event analysis, and prespecified thresholds. No salivary marker replaces biopsy of a suspicious lesion [9,10,11,13].

4.2 Dental Caries

Caries is a biofilm-mediated, sugar-driven disease modified by saliva, fluoride, tooth substrate, behavior, and social context. Flow, pH, buffering, calcium, phosphate, and fluoride influence demineralization–remineralization. Mutans streptococci and lactobacilli counts support risk estimation but have limited lesion specificity; carriage can occur without active disease and community ecology matters [14,15,16].

Host candidates include alpha-amylase, carbonic anhydrase VI, proline-rich proteins, mucins, statherin, cystatins, immunoglobulins, defensins, LL-37, histatin-5, lactoferrin, and calprotectin.

Findings vary by age, dentition, sampling, and disease definition. Proteomic and metabolomic profiles separate high- from low-caries groups in discovery datasets, but independent validation against contemporary lesion-activity standards is rare. Current use is therefore risk assessment alongside prior caries, diet, fluoride, plaque, social factors, and examination—not stand-alone lesion diagnosis. The decisive design is prospective prediction of incident or progressing non-cavitated lesions with incremental value over a validated clinical model [14,15,16].

4.3 Periodontal Diseases

Periodontitis reflects dysregulated host responses to dysbiotic biofilm and is diagnosed by attachment loss, probing depths, bleeding, and radiographic bone loss. Saliva pools multiple sites and is convenient for patient-level screening but cannot localize an active pocket. IL-1β, IL-6, IL-8, TNF-α, MMP-8, MMP-9, calprotectin, S100 proteins, C-reactive protein, and bone-turnover mediators are commonly elevated. Gingivitis shares inflammatory pathways, so the crucial discrimination is reversible inflammation versus destruction [17,18].

MMP-9, IL-1β, and inflammatory–microbial panels may improve discrimination. RANKL promotes osteoclastogenesis and osteoprotegerin (OPG) is a decoy receptor, but salivary dilution produces inconsistent RANKL/OPG findings. Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, and dysbiosis panels add etiological information but cannot distinguish colonization from current destruction. Proteomics repeatedly identifies S100A8, complement C3, profilin-1, and fibrinogen; pooled S100A8 discrimination is only modest (AUC about 0.71). Biomarker declines after therapy are plausible monitoring signals, but utility requires evidence that biomarker-guided recall improves outcomes beyond probing and bleeding scores [17,18].

Table 2. Caries and periodontal biomarkers

Disease	Candidate markers	Evidence	Current utility
Caries	Flow, pH, buffering, microbes, amylase, peptides, omics	Heterogeneous associations	Adjunctive risk assessment
Gingivitis	IL-1β, IL-6, IL-8, MMP-8	Often elevated; overlaps with periodontitis	Inflammatory monitoring
Periodontitis	aMMP-8, MMP-9, IL-1β, S100A8, RANKL/OPG, dysbiosis	MMP-8 most replicated; POC accuracy moderate	Adjunct to examination
Therapy response	aMMP-8, cytokines, microbial panels	Often decline after therapy; decision benefit unknown	Research/selected monitoring

4.4 Oral Inflammatory and Autoimmune Diseases

OLP studies evaluate IL-4, IL-6, IL-8, TNF-α, cortisol, nitric oxide, oxidative markers, miR-21, and miR-27b. Meta-analyses support altered group means, but subtype, stress, treatment, periodontitis, and diagnostic confirmation limit specificity. Cortisol may describe stress-axis activity rather than OLP. miRNA overlap between OLP and OSCC is interesting but clinically problematic unless a panel distinguishes inflammation from dysplasia [8,19,20].

In Sjögren syndrome the salivary gland is a primary target. Flow, autoantibodies, β2-microglobulin, cathepsins, cytokines, calprotectin, lactoferrin, proteomic/metabolomic signals, regulatory RNAs, and EV cargo have been investigated. Recurrent candidates include lactate, alanine, taurine, neutrophil gelatinase-associated lipocalin, β2-microglobulin, annexin A2, and selected RNAs. Current classification integrates symptoms, serology, ocular tests, flow, imaging, and sometimes minor-gland biopsy. Salivary panels may reduce delay or

stratify activity, but no analyte replaces that multimodal pathway [21,22].

4.5 Other Oral Conditions

Salivary amplification can identify viral, fungal, and bacterial nucleic acid, but detection may represent carriage rather than invasive infection. Peri-implant mucositis and peri-implantitis studies report IL-1β, MMP-8, MMP-9, RANKL/OPG, and microbial shifts. Saliva is convenient for whole-mouth surveillance but loses site specificity; peri-implant crevicular fluid may better reflect one implant. Evidence does not support saliva-only diagnosis. Temporomandibular disorder studies report cortisol, alpha-amylase, cytokines, and pain metabolites, all influenced by stress, sleep, circadian rhythm, and comorbid pain. Similar oxidative, hormonal, inflammatory, and omics signals in aphthous disease, burning mouth, mucositis, and bruxism remain exploratory [23].

5. Omics Approaches in Salivary Biomarker Discovery

Proteomics uses mass spectrometry or affinity platforms to identify abundance and post-translational change. Abundant amylase and mucins can mask low-abundance proteins; depletion, digestion, instrument, database, and normalization affect results. Targeted mass spectrometry or immunoassay is required for verification. Transcriptomics detects host and microbial RNA; genomics and epigenomics assess mutation, copy number, methylation, and microbial genes. Sequencing requires stabilization, batch correction, and independent qPCR or digital-PCR confirmation [3,13,25].

Metabolomics and lipidomics use nuclear magnetic resonance or mass spectrometry to measure small molecules and lipids. They closely reflect phenotype but are dominated by diet, microbiota, fasting, and time. Microbiomics now includes 16S sequencing, shotgun metagenomics, metatranscriptomics, and functional profiling; compositional methods are essential because relative abundance can change without absolute increase. EV analysis may enrich stable RNA and protein but needs standardized isolation, purity, particle counting, and nomenclature [3,25].

Multi-omics can combine complementary biology by early fusion, late fusion, or networks. The main risk is dimensionality exceeding sample size. Feature selection before cross-validation and data leakage during normalization inflate AUC. A defensible pipeline separates discovery and locked validation, resamples participants rather than aliquots, reports calibration, and tests portability across centres and platforms [24,25].

6. Diagnostic Accuracy and Clinical Utility

Sensitivity is the proportion of diseased participants testing positive; specificity is the proportion without disease testing negative. Predictive values depend on prevalence, so impressive case-control results may generate many false positives in low-prevalence screening. ROC/AUC describes rank discrimination across thresholds but not calibration, consequences, or performance at the selected cut-off. Diagnostic odds ratios summarize separation but can conceal imbalance [25].

Panels often outperform single markers because biology is heterogeneous, but adding variables improves apparent training performance even without transportability. Penalization, nested cross-validation, prespecified thresholds, and external validation are essential. Controls must represent clinical alternatives: benign and inflammatory lesions for OSCC, gingivitis for periodontitis, and future lesion development beyond established caries risk. Decision-curve analysis can quantify whether testing improves biopsy or recall decisions [6,18,24].

Discovery identifies a signal; analytical validation establishes precision, linearity, limits, interference, stability, and reproducibility; clinical validation measures

intended-use performance; clinical utility demonstrates improved decisions or outcomes; implementation adds usability, economics, quality control, and regulation. Most salivary markers remain between discovery and early clinical validation. aMMP-8 is a partial exception because commercial formats and multiple studies exist, but moderate accuracy keeps it adjunctive [18].

Table 3. Advantages and limitations

Domain	Advantages	Limitations/mitigation
Collection	Non-invasive and repeatable	Standardize timing, device, duration, flow
Biological proximity	Direct exposure to oral lesions	Inflammation/blood reduce specificity
Assays	Compatible with immunoassay, PCR, omics	Viscosity, proteases, low abundance
Clinical use	Chairside triage/risk/monitoring	Prevalence-dependent predictive values
Research	Longitudinal multi-omics feasible	Small samples, batch effects, overfitting
Implementation	Potentially improves access	Regulation, cost, privacy, equity

7. Factors Affecting Salivary Biomarker Levels

Age, sex, dentition, hormonal state, diet, hydration, smoking, tobacco, alcohol, hygiene, medication, systemic disease, infection, exercise, stress, and sleep can change flow or composition. Diabetes and obesity can increase inflammation and are associated with periodontitis, creating confounding. Anticholinergic and psychotropic drugs reduce flow; steroids alter cytokines; probing or brushing can introduce blood. Smoking may suppress visible gingival inflammation while altering molecular profiles [17,25].

Circadian rhythms are prominent for cortisol and melatonin. Flow changes concentration even when secretion is stable. Stimulated and unstimulated samples are not interchangeable. Tubes, swabs, centrifugation, temperature, delay, storage, freeze–thaw, and stabilizers may selectively alter analytes. Post-collection microbial growth and reagent contamination are critical for microbiome studies. These variables should be measured and addressed by design; statistical adjustment cannot rescue poorly captured confounding [25].

8. Current Challenges and Limitations

Lack of standardization spans disease definitions, sampling, processing, assays, units, normalization, and thresholds. Small samples and multiple testing create false discovery; healthy-only controls cause spectrum bias; retrospective selection and missingness cause selection bias; lack of blinding causes review bias. Many models report AUC without confidence intervals, calibration, threshold-specific confusion matrices, or external validation. False positives can cause anxiety and unnecessary biopsy; false negatives can delay cancer care [6,25].

Shared inflammation limits attribution: elevated IL-8 may reflect OSCC, periodontitis, infection, tobacco, or combinations. Omics remain costly and bioinformatically demanding, while chairside devices must retain performance across operators and temperatures. Regulation requires a defined intended use, reproducible manufacturing, analytical and clinical evidence, surveillance, and governance. AI adds privacy, bias, explainability, and dataset-shift concerns [2,24].

9. CONCLUSION

Saliva provides an accessible window into oral host, microbial, and lesion biology. The most consistent evidence concerns inflammatory cytokines and tissue-remodeling enzymes in OSCC and periodontal disease, with aMMP-8 closest to chairside translation. Cancer-related protein panels, nucleic acids, metabolites, microbiome signatures, and EV cargo are compelling, but most estimates derive from discovery or case-control settings and do not

justify stand-alone diagnosis or screening. Caries and immune-mediated disease markers currently offer risk or mechanistic information rather than replacement tests. Progress requires standardized preanalytics, intended-use populations, locked assays and thresholds, external prospective validation, transparent accuracy and calibration, and proof that testing improves outcomes. Salivary diagnostics should therefore be framed as adjunctive technology with substantial future potential and clear present limitations.

Declaration by Authors

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