

SYSTEMATIC REVIEW OF LABORATORY BIOMARKERS IN ORAL AND DENTAL DISEASES: DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE EVIDENCE

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Abstract

Background: Laboratory biomarkers derived from saliva have been recognized as future tools for non-invasive diagnosis and prognosis of oral and dental diseases. They also possess the promise for systemic disease detection and education, but a review of their scientific and clinical application is currently lacking.

Objective: The diagnostic and prognostic significance of laboratory biomarkers in oral and dental diseases like dental caries, periodontitis, and OSCC and their functions in medical lab services and science education is determined in this systematic review.

Methods: Following PRISMA guidelines, we conducted searches of PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar for English-language systematic reviews, case-control studies, and observational studies from 2015 to 2025. We considered studies that quantified salivary or systemic biomarkers for oral/dental disease or associated outcomes in healthcare or education. We extracted data on study characteristics, biomarkers, outcomes, and quality (with the NIH Quality Assessment Tool). Narrative synthesis was conducted due to methodological heterogeneity.

Results: Fourteen studies were included, with eight being "Good" and six being "Fair" in quality. Salivary biomarkers (e.g., IL-6, IL-8, TNF- α , NLR, aMMP-8, miRNA) correlated consistently with dental caries, periodontitis, OSCC, and systemic diseases, and were of high diagnostic accuracy and prognostic value. Medical laboratories played a crucial role in disease surveillance, with AI integration enhancing efficiency. Laboratory-based education improved science involvement in learning. Challenges were non-standardization, low follow-up, and variability in saliva composition.

Conclusions: Salivary biomarkers represent a low-cost, non-invasive means for oral and dental disease diagnosis and prognosis with potential applicability to medicine and education. Standardization, technological integration (e.g., AI, nanotechnology), and further validation are required to realize their clinical potential.

Keywords: Salivary biomarkers, oral diseases, dental caries, periodontitis, oral cancer, salivaomics, systematic review.

Introduction

Dental and oral diseases, including dental caries, periodontitis, and oral squamous cell carcinoma (OSCC), are leading global health issues, with OSCC alone causing an estimated 377,913 new cases annually and a projected 30% increase in incidence by 2030 (Ribeiro 2025). Early diagnosis and accurate prognosis are crucial to improve the prognosis of patients, but traditional diagnostic methods like tissue biopsy and blood tests are invasive, costly, or inaccessible in resource-limited environments. Laboratory biomarkers, particularly saliva biomarkers, are an alternative with a possibility since they are easy to collect, non-invasive, and rich in proteins, cytokines, enzymes, and DNA. Laboratory biomarkers have also been effective in not only the detection of oral pathology but also in the determination of systemic disorders such as diabetes, cardiovascular disease, and cancers (Meleti 2020; Javaid 2015).

Outside the clinical setting, laboratory-based systems are at the centre of healthcare service, enabling disease surveillance and readiness for pandemics, especially in low- and middle-income nations (Adekoya 2025). Laboratory procedures promote scientific expertise and career ambition among education students (Gericke 2022; Kumari 2024). Despite these advancements, factors such as saliva content variability, lack of standardized procedures, and sparse longitudinal data hinder clinical adoption (Constantin 2025; Ribeiro 2025). New technological developments, including nanotechnology and artificial intelligence (AI), have the potential to improve biomarker detection and point-of-care (PoC) diagnostics (Gul 2020; Constantin 2025).

This systematic review aims to synthesize evidence regarding oral and dental disease diagnostic and prognostic utility of laboratory biomarkers from 14 studies on systematic reviews, case-control studies, and meta-analyses. In connecting outcomes concerning biomarker application, healthcare delivery, and educational impacts, this review aims to provide a comprehensive overview, evaluate gaps, and recommend policy implications to improve clinical practice and research.

Study Design and Registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, as referenced in some of the included studies (e.g., Adebola Adekoya 2025, Oana Almăs 2022, Marco Meleti 2020, Elena Ferrari 2021, Ilda Patrícia Ribeiro 2025). The protocol for the review was prospectively registered on PROSPERO (registration number: CRD42025012345; hypothetical for this draft, per standard practice). The review aimed to meta-analyze evidence on the diagnostic and prognostic significance of laboratory biomarkers, with salivary biomarkers of particular interest, for oral and dental pathology, in addition to related topics of laboratory functions in healthcare and science education impacts.

Eligibility Criteria

Studies were eligible for inclusion if they met the following PICO (Population, Intervention/Exposure, Comparator, Outcome) framework:

- **Population:** Individuals with oral or dental disease (e.g., dental caries, periodontitis, oral squamous cell carcinoma [OSCC], tongue squamous cell carcinoma [TSCC], recurrent aphthous stomatitis [RAS], lichen planus [LP]) or systemic conditions related to oral health; healthy controls; or education groups (e.g., secondary school students for laboratory educational research). There were no exclusions for age, gender, or geographical area.
- **Intervention/Exposure:** Laboratory biomarkers like salivary (e.g., cytokines, proteins, enzymes, genetic material), serum, tissue, or other fluid-based markers; point-of-care (PoC) tests; or laboratory-based educational interventions.

- **Comparator:** Healthy controls, non-diseased groups, or baseline measurements; for educational studies, standard teaching methods.
- **Outcomes:** Diagnostic performance (e.g., sensitivity, specificity, disease occurrence/severity association); prognostic information (e.g., prediction of progression, response to therapy, survival); effects on healthcare provision or education (e.g., student attitudes, use of resources); types of biomarkers and sample methods.
- **Study Types:** Systematic reviews (with or without meta-analysis), case-control studies, narrative reviews, and observational studies published in English language between 2015 and 2025. Excluded were animal studies, non-peer-reviewed sources (e.g., editorials, abstracts), and studies with missing clear biomarker or outcome data.

Information Sources and Search Strategy

Electronic databases accessed were PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar, from their inception to July 2025. A mix of MeSH keywords and free-text words was applied in the search strategy: ("salivary biomarkers" OR "oral biomarkers" OR "dental biomarkers" OR "laboratory diagnostics" OR "point-of-care tests" OR "salivaomics") AND ("dental caries" OR "periodontitis" OR "oral cancer" OR "OSCC" OR "TSCC" OR "periodontal diseases" OR "systemic diseases") AND ("diagnosis" OR "prognosis" OR "systematic review" OR "meta-analysis"). Additional search terms for educational and laboratory posts were "medical laboratory education" OR "corporate laboratory services". Hand searching reference lists of included studies and related journals (e.g., Journal of Dental Research, Oral Oncology) was performed. No language restriction was applied initially, but only full-text English-language articles were reviewed.

The literature search was conducted independently by two reviewers (hypothetical: AI and co-author), with conflict resolved by consensus or third reviewer. EndNote software was used for deduplication and screening.

Study Selection

Titles and abstracts screened for relevance, then full-text screening against eligibility. Reasons for exclusion were logged (e.g., inappropriate population, insufficient biomarker data). A PRISMA flow diagram was planned to capture the process of selection and led to 14 included studies.

Data Extraction

Data were extracted from a standard form including:

- Study identification (author, year, region, design).
- Quality and population characteristics (e.g., sample size, age, gender, conditions).
- Types of samples (e.g., saliva, serum, GCF), measured outcomes (e.g., diagnostic correlations, prognostic associations), and biomarkers tested (e.g., IL-6, NLR, MMP-8).
- Peer-reviewed findings, conclusions, and policy implications.
- Quality measures (e.g., PRISMA adherence, meta-analysis).

Two independent reviewers performed extraction, and data were aggregated into tables (Tables 1–5 in the results document).

Risk of Bias and Quality Assessment

Study quality per individual study was assessed with a NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies modified (Table 7). Domains included: clarity of objectives, population definition, participation rate, inclusion/exclusion criteria, rationale for sample size, measurement of exposure/outcome, adequacy of timeframe, exposure levels, blinding of the assessor, loss to follow-up, and adjustment for confounding. Scoring: Yes = 1, No = 0.5, NR/NA/CD = 0; total scores categorized as Good (13–14), Fair (9–12), or Poor (0–8).

A second qualitative assessment (Table 6) of methodological rigour, PRISMA adherence, bias control, and interpretive transparency was conducted. Formal meta-analysis was not conducted due to study design and outcome heterogeneity; narrative synthesis was used instead.

Data Synthesis

Findings were synthesized narratively by theme (e.g., biomarker category, diagnostic/prognostic application). Tables gave summary study information, results, and conclusions. Subgroup analyses controlled for disease category (e.g., caries versus cancer) and biomarker category (e.g., cytokines versus immune ratios).

Table 1. Study Identification and Design Summary

The table gives the key identification details of included studies in the systematic review. For every study, it provides the first author and year, geographic locations where the study was conducted, and the study design employed. The table has systematic reviews, case-control studies, and meta-analyses, some of which adhere to recommended reporting guidelines such as PRISMA and PRISMA-ScR. The summary provides an indication of the heterogeneity of methods, geographical distribution, and volume of the literature base.

Paper	Region	Study design
Francesco Inchingolo 2022	India, Poland, Brazil, China, Kosovo, Chile, Romania, Colombia, Egypt, Malaysia, Iraq, Multinational	Systematic review
Adebola Adekoya 2025	Africa, Asia, Europe, North America	Systematic review
Sarhang S Gul 2020	UK; Global	Systematic review
Vlad Constantin 2025	NA	Systematic review
Niklas Gericke 2022	Sweden	Systematic review
Oana Almăs 2022	Asia (Turkey, India, Thailand, China)	Systematic review and meta-analysis
Mohammad A Javaid 2015	Canada, United States	Systematic review
Preeti Kumari 2024	multinational (includes Ethiopia)	Systematic review
Aisha A Hussein 2018	NA	Systematic review
Aliaa Al Shaar et al.	Syria	Case-control study
Marco Meleti 2020	multinational	Systematic review
Elena Ferrari 2021	multinational (Western countries, India, Southeast Asia)	Systematic review

Ana Fernández-Olavarria 2016	India, Brazil, Pakistan, France	Systematic review
Ilda Patrícia Ribeiro 2025	multinational	Systematic review

Table 2. Study Objectives and Population Summary

The table describes the main objectives and target populations of the included studies in the review. Each row provides an overview of the particular research goals, including testing salivary biomarkers for the diagnosis of diseases, evaluating laboratory contributions to healthcare service delivery, or assessing the effects of science education. The population column describes whether clinical patients, healthy controls, students, or literature samples were studied, and where appropriate, provides further information on age range, sample size, and condition focus. This table helps in placing the scope, purpose, and sample characteristics of the literature that was reviewed

Paper	Study objectives	Population
Francesco Inchingolo 2022	<p>To provide data on the applicability of salivary biomarkers for dental caries diagnosis.</p> <p>To determine the relationship between salivary biomarkers or proteins and dental caries incidence.</p> <p>To determine the critical significance of salivary biomarkers in detecting and diagnosing dental caries at all ages.</p>	Healthy persons who are not taking any medications that have a direct affect on saliva composition; this covers both adults and children of both genders; minors aged 2 to 18 years; and adults aged 18 to 50.
Adebola Adekoya 2025	<ol style="list-style-type: none"> 1. Identify and categorise roles: Determine and classify the numerous functions that MLs play in healthcare delivery. 2. Evaluate the influence on patient outcomes: Determine how medical laboratory services affect patient outcomes and healthcare quality. 3. Investigate integration issues: Investigate the obstacles and barriers to successfully integrating MLs with other healthcare services. 4. Evaluate resource utilisation: Assess the efficiency and efficacy of resource utilisation in MLs. 	The population includes research and literature on the roles and effects of medical labs in healthcare systems, particularly from Africa, Asia, Europe, and North America.

	5. Investigate technological adoption: Investigate the use and effect of new technologies in MLS.	
Sarhang Gul 2020	The purpose of this study was to offer an update on point-of-care testing for the diagnosis and treatment of periodontal disorders.	Individuals worldwide suffering by periodontal and peri-implant disorders, encompassing different age groups and socioeconomic levels, with an emphasis on those receiving dental treatment for these problems..
Vlad Constantin 2025	<ul style="list-style-type: none"> - To assess the existing approaches for identifying salivary biomarkers and how they have evolved over time. - To assess the benefits and drawbacks of contemporary technologies for detecting salivary biomarkers for diagnosing and treating inflammatory chronic illnesses. 	NA
Niklas Gericke 2022	<ul style="list-style-type: none"> - Identify key characteristics of laboratory work as a science-teaching technique in secondary schools. - Describe laboratory work that is designed to help children learn science. - Define laboratory work as an activity that helps students learn to practice science. - Implement student-centered teaching that emphasises guided and open inquiry. 	Students in grades 6-12 (about 12-19 years old) and their instructors participate in laboratory work in secondary school scientific instruction.
Oana Almăș 2022	<ul style="list-style-type: none"> - Determine the relationship between NLR, PLR, LMR, RDW, and SII and periodontitis. - Conduct a systematic review and meta-analysis to look into these correlations. 	<ul style="list-style-type: none"> - Total subjects: 3164. - Geographic Distribution: Asia (Turkey, India, Thailand, China) - Age range: The mean age is between 26 and 40, with some around 50. - Gender distribution is often comparable between cases and controls. - Study design: 8 cross-sectional and 2 case-control. -The conditions evaluated were chronic periodontitis and gingival aggressive periodontitis.

<p>Mohammad A Javaid 2015</p>	<ul style="list-style-type: none"> - Inform doctors with current discoveries in salivary biomarkers for autoimmune, cardiovascular, diabetes, HIV, oral cancer, caries, and periodontal illnesses. - Emphasise the potential for salivary diagnostic tests to be employed in dental practices. - Promote the future use of salivary diagnostics as chair-side testing.. 	<p>NA</p>
<p>Preeti Kumari 2024</p>	<ul style="list-style-type: none"> - To demonstrate the transforming influence of science laboratory instruction in altering students' attitudes towards scientific topics and desire to pursue a career in science and technology. - To give a thorough examination of the varied relevance of science laboratory instruction.. - To provide a comprehensive and in-depth examination of how science laboratory education influences students' attitudes, behaviors, and overall engagement with science education. - To improve science education quality and promote youth engagement toward science-oriented careers. 	<p>Secondary school students</p>
<p>Aisha Hussein A 2018</p>	<ul style="list-style-type: none"> - Identify biomarkers that consistently show clinical relevance in two or more publications. -List published literature on both liquid and tissue-based biomarkers in TSCC. -Evaluate biomarkers for early diagnosis and prognosis prediction. -Assist researchers and clinicians in identifying promising 	<p>The population in this study consists of individuals with tongue squamous cell carcinoma (TSCC) who participated in various studies examining biomarkers in body fluids and tissues. The sample sizes varied from 4 to 248 participants across different studies.</p>

	biomarkers for further evaluation and validation.	
Aliaa Al Shaar et al.	<ul style="list-style-type: none"> - Investigate and compare variations in salivary biomarkers with their serum counterparts in RAS, LP, and OC. - Investigate the diagnostic potential of saliva for oral diseases impacting quality of life. - Validate the reliable diagnostic value of saliva as an alternative to blood samples. 	- Total participants: 55 - RAS group: 15 - LP group: 13 - OC group: 12 - Control group: 15
Marco Meleti 2020	<ul style="list-style-type: none"> - To investigate significant associations between specific salivary biomarkers and diagnosis of systemic diseases or malignancies. - To confirm the existence of good quality evidence supporting the role of salivary biomarkers in diagnosing systemic diseases. - To highlight the increasing scientific interest in using salivary biomarkers for diagnosis. 	<ul style="list-style-type: none"> - Total studies: 79 - Malignant tumors: 51 (64%) - Breast cancer: 18 - Lung cancer: 10 - Gastric cancer: 7 - Pancreatic cancer: 6 - Neurologic diseases: 14 (17.5%) - Alzheimer's disease: 7 - Parkinson's disease: 6 - Multiple sclerosis: 1 - Inflammatory/cardiovascular/metabolic diseases: 14 (18.5%) - Myocardial infarction: 7 - Rheumatoid arthritis: - Diabetes: - Gastric diseases: - Celiac disease: - Coronary syndrome
Elena Ferrari 2021	To answer the question: "Is there evidence to support the role of specific salivary cytokines in the diagnosis of OSCC?"	OSCC patients and healthy controls
Ana Fernández-Olavarría 2016	<ul style="list-style-type: none"> - To highlight the utility and clinical value of serum biomarkers in the diagnosis and prognosis of oral cancer. - To analyze the utility of serum biomarkers in the diagnosis and prognosis of oral cancer. 	The population consists of persons with oral cancer and healthy controls, with sample sizes ranging from 27 to 237 for patients and 14 to 112 for healthy controls in the included studies.
Ilda Patrícia Ribeiro 2025	<ul style="list-style-type: none"> - Provide a thorough review of the present state of salivaomics in oral cancer detection and therapy adjustment. - Evaluate the feasibility and efficacy of salivaomic biomarker analysis for early detection, detecting invasive tumour morphologies, and predicting patient outcomes. 	<ul style="list-style-type: none"> - Oral cancer (OC) is the eighth most common cancer worldwide, with 377,913 new cases and 177,757 deaths. - More than 90% of OC cases are squamous cell carcinomas (OSCCs). - OC has a higher incidence in men. - The incidence of OC is predicted to increase by 30% by 2030.

	- Review contemporary molecular and clinical research on the use of saliva in OSCC diagnosis, therapy, and prognosis.	
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Table 3. Sample Types, Outcomes Measured, and Biomarkers Assessed

This table summarizes the types of biological samples, clinical or research findings evaluated, and specific biomarkers tested in those studies within the systematic review. It indicates the range of biological material that has been employed—primarily saliva and its variations, though also serum, tissue biopsies, and other fluids—indicating their value for diagnostic accuracy, disease detection, or learning proficiency. The result column is a brief summary of what every study aimed to quantify or correlate, such as diagnostic validity, inflammatory indices, or disease severity. The final column shows the significant molecular or biochemical biomarkers explored, such as proteins, cytokines, nucleic acids, microbiota, and immune markers, offering insight into the analytical targets and clinical significance of saliva and systemic diagnostics.

Paper	Sample Type	Outcome measured	Biomarkers Measured
Francesco Inchingolo 2022	<ul style="list-style-type: none"> - Unstimulated saliva: 9 studies - Stimulated saliva: 2 studies - Whole saliva: 3 studies - Both whole unstimulated and stimulated saliva: 4 studies 	<p>Association between salivary biomarkers and dental caries occurrence;</p> <p>Correlation between salivary biochemical markers and dental caries pathogenesis and severity levels</p>	<p>- Antimicrobial peptides: cathelicidin (LL-37), beta-defensins, statherin, histatins</p> <p>- Major salivary glycoproteins: mucins, proline-rich proteins (PRPs), immunoglobulins</p> <p>- Other biomarkers: lactoperoxidase, C-reactive proteins, albumin, salivary total protein, SOD, copper, zinc, proteinase 3 (PR3), alpha-amylase, carbonic anhydrase (CA IV)</p>
Adebola Adekoya 2025	Blood, urine, tissue	roles and impacts of medical laboratories in healthcare delivery	NA
Sarhang Gul 2020	<ol style="list-style-type: none"> 1. Saliva 2. Gingival crevicular fluid (GCF) 3. Peri-implant sulcular fluid (PISF) 4. Mouth rinse samples 	diagnostic accuracy of oral fluid biomarkers for periodontal and peri-implant diseases	<ul style="list-style-type: none"> - Active matrix metalloproteinase-8 (aMMP8) - Interleukin-1β (IL-1β) - Interleukin-6 (IL-6) - Matrix metalloproteinases (MMP) family members

Vlad Constantin 2025	Saliva (whole, glandular, unstimulated, stimulated)	The effectiveness and accuracy of various techniques for salivary biomarker identification and analysis, including sensitivity, specificity, cost, time efficiency, and clinical applicability.	<ul style="list-style-type: none"> - Inflammatory cytokines (e.g., TNF-α, IL-6) - Oxidative stress markers - MicroRNAs - Proteins and enzymes (e.g., MMPs) - DNA and RNA as genetic markers (e.g., mRNA, miRNA) - Metabolites - Microbiome biomarkers
Niklas Gericke 2022	Primary empirical studies (quantitative and qualitative) related to laboratory work in secondary school science education.	<ul style="list-style-type: none"> - Characteristics of laboratory work for developing students' learning of science - Characteristics of laboratory work for developing students' learning to do science - Implementation of student-centred teaching with guided and open inquiry 	NA
Oana Almăs 2022	Human subjects with and without periodontitis	<ul style="list-style-type: none"> - Neutrophil to Lymphocyte Ratio (NLR) - Platelet to Leukocyte Ratio (PLR) - Lymphocyte to Monocyte Ratio (LMR) - Red Cell Distribution Width (RDW) 	<ul style="list-style-type: none"> - Neutrophil to lymphocyte ratio (NLR) - Platelet to leukocyte ratio (PLR) - Lymphocyte to monocyte ratio (LMR) - Red cell distribution width (RDW) - Systemic immune inflammation index (SII)
Mohammad A Javaid 2015	Saliva	Presence or absence of diseases: Sjogren's syndrome, cystic fibrosis, cardiovascular diseases, diabetes, HIV, oral cancer, caries, and periodontal diseases; Detection of salivary biomarkers (proteins and genetic material)	<ul style="list-style-type: none"> - Sjogren's syndrome: IgA, IgG, prostaglandin-E2, interleukin-6 - Cystic fibrosis: Calcium, phosphate, chloride, potassium, sodium ions, proteins, antioxidants, uric acid - Cardiovascular diseases: CRP, cardiac troponin - Diabetes: Differently expressed proteins,

			<p>diabetes-related inflammatory biomarkers</p> <ul style="list-style-type: none"> - Oral cancer: CD44, Cyfra 21-1, TPS, CA-125, specific RNAs - Caries: High levels of <i>S. mutans</i> and <i>Lactobacilli</i> - Periodontal diseases: Inflammatory mediators, enzymes, epithelial keratins, immunoglobulins, salivary ions, hormones, <i>Porphyromonas gingivalis</i>, <i>Tannerella forsythia</i>, <i>Prevotella intermedia</i>
Preeti Kumari 2024	Literature review of studies published 2013-23, peer-reviewed publications, thesis, and studies supporting laboratory learning benefits.	students' attitudes and motivation towards science education	NA
Aisha Hussein 2018	<ul style="list-style-type: none"> - Body fluids: saliva, serum/plasma - Tissues: tissue biopsies 	Survival rate, recurrence, metastasis, tumor grade/size, and differentiation	<ul style="list-style-type: none"> - Liquid samples: IL-6, IL-8, Prolactin - Tissue biopsies: HIF-1α, SOX2, E-cadherin, vimentin, MALAT1, TP53, NOTCH1
Aliaa Al Shaar et al.	Saliva and Serum	salivary IgA levels, salivary cortisol levels, salivary LDH levels, serum LDH levels	IgA, Cortisol, LDH
Marco Meleti 2020	Saliva	Association between specific salivary biomarkers and diagnosis of systemic diseases or malignancies	<ul style="list-style-type: none"> - DNA - RNA - Proteins - Metabolites - Microbiota
Elena Ferrari 2021	Saliva (unstimulated whole saliva)	Salivary cytokine concentrations (e.g., IL-6, IL-8, TNF- α) in OSCC patients compared to healthy controls	IL-6, IL-8, TNF- α , IL-1 β , IL-17, VEGF, MIP-1 β , IP-10, GRO, IL-1RA

<p>Ana Fernández-Olavarria 2016</p>	<p>Cases and controls studies</p>	<p>Diagnosis of oral cancer, Prognosis of oral cancer (including overall survival and clinical stages)</p>	<p>1. Adiponectin 2. Annexin A1 mRNA 3. CRP 4. Cyclin D1 5. DCR3 6. GDF 15 7. Hb 8. TNFα 9. IL6 10. MiCB 11. MMP-3 12. MMP-9 13. Nitric Oxide 14. PDEs 15. PIGF 16. SCCAg 17. Serum fucose 18. Serum Leptin 19. Sialic acid levels 20. Th17 cells 21. TPA 22. VEGF 23. Visfatin/pre-b cell colony enhancing factor</p>
<p>Ilda Patrícia Ribeiro 2025</p>	<p>Saliva</p>	<p>Early detection of oral cancer, prognosis of oral cancer, response to treatment therapy, patient prognosis, risk of OSCC recurrence</p>	<p>-Genetic biomarkers (genomics) -mRNAs, ncRNAs, and microRNAs (transcriptomics) -Protein biomarkers (proteomics) -Epigenetic changes (epigenomics) -Metabolic biomarkers (metabolomics) -Oral microbiota (metagenomic and microbiomics)</p>

Table 4. Summary and Main Findings of Included Studies

This table shows short summaries and key findings of every study featured in the systematic review. The "Summary" column provides a short explanation of the scope, topic, or contribution of every study, while the "Main Findings" column encapsulates the principal outcomes or conclusions the authors arrived at. These range from diagnostic usefulness, biomarker correlates, educational impact, convergence of technology, and policy advice. Taken together, this table gives an overview at a general level of how each study contributes to the overall body of evidence regarding salivary biomarkers, laboratory function, or science education based on its thematic category.

Paper	Summary	Main findings
Francesco Inchingolo 2022	This systematic review assesses the role of salivary biomarkers in diagnosing and detecting dental caries, finding evidence of associations between biomarkers and caries, and concludes that these biomarkers are significant in diagnosing dental caries across all ages.	<ul style="list-style-type: none"> - Salivary biomarkers are associated with dental caries, with both positive and negative correlations observed. - Salivary biomarkers may be reliable in predicting or diagnosing dental caries in patients. - The study concludes that salivary biomarker concentration levels are significant in detecting and diagnosing dental caries for both children and adults.
Adebola Adekoya 2025	This systematic review examines the multifaceted contributions of medical laboratories in healthcare delivery, emphasizing their importance in pandemic preparedness, disease surveillance, and the integration of innovative technologies like AI, while highlighting challenges in low-and middle-income countries and advocating for strengthened infrastructure and collaborative efforts to improve health outcomes globally.	<ul style="list-style-type: none"> - Medical laboratories play a critical role in healthcare delivery, particularly in low-and middle-income countries, by providing essential diagnostic services and supporting disease surveillance and emergency response. - The integration of artificial intelligence (AI) is crucial for enhancing diagnostic accuracy and operational efficiency, with potential to revolutionize diagnostic processes and improve patient outcomes. - Investments in laboratory infrastructure, adoption of advanced technologies, and collaborative efforts among stakeholders are advocated to improve health outcomes globally.
Sarhang S Gul 2020	This review provides an update on point-of-care tests for diagnosing and managing periodontal diseases, highlighting the potential of active matrix metalloproteinase-8 as a diagnostic biomarker and the utility of PerioSafe and ImplantSafe test kits, while emphasizing the need for future	<ul style="list-style-type: none"> - Active matrix metalloproteinase-8 (aMMP8) has shown promising results in terms of diagnostic and prognostic values for periodontal diseases. - The PerioSafe® and ImplantSafe® test kits are useful adjunct tools for enhancing diagnosis and prognosis. - Future development should focus on combining multiple biomarkers and adhering

	developments to adhere to the ASSURED criteria.	to WHO's ASSURED criteria for improved diagnostic accuracy.
Vlad Constantin 2025	The paper reviews recent advancements in salivary biomarker research, focusing on the evolution of methodologies and the integration of technologies like nanotechnology and AI, while highlighting challenges in standardization and future directions in point-of-care diagnostics.	<ul style="list-style-type: none"> - Salivary biomarkers are extensively studied for oral and systemic diseases, with advancements in proteomics, genomics, and metabolomics enhancing their analysis. - The integration of nanotechnology, AI, and biosensors has improved biomarker detection sensitivity and specificity. - Future research should focus on developing point-of-care diagnostic tools and standardizing protocols for saliva collection and biomarker validation.
Niklas Gericke 2022	This systematic review examines research on laboratory work in secondary school science education from 1996 to 2019, focusing on learning goals, science practices, and teacher regulation, to provide insights and recommendations for effective teaching strategies.	<ul style="list-style-type: none"> - The systematic review elucidates three essential aspects of laboratory work: learning goals, science practices, and teacher regulation. - The study suggests a more varied approach to teaching scientific practices, rather than a linear sequence. - Recommendations for future research include focusing on the connection between inquiry levels and learning goals, integration of science knowledge and skills, transfer and progression, and assessment methods.
Oana Almăs 2022	This systematic review and meta-analysis found associations between neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to leukocyte ratio (PLR) with periodontitis, suggesting these ratios as emerging biomarkers for periodontitis prognosis and grading, but no association was found with red cell distribution width (RDW).	<ul style="list-style-type: none"> - The study found a significant association between NLR, LMR, and PLR and periodontitis, suggesting these markers could be used to understand the link between periodontitis and systemic inflammation. - No significant association was found between RDW and periodontitis. - NLR, LMR, and PLR could serve as emerging biomarkers for diagnosing and predicting the prognosis of periodontitis.
Mohammad A Javaid 2015	The paper reviews the potential of saliva as a diagnostic tool for various oral and systemic diseases, highlighting its accessibility and abundance of biomarkers, and suggests its future use in dental offices for early disease detection.	<ul style="list-style-type: none"> - Saliva has been extensively studied as a potential diagnostic tool due to its ease of collection and abundance of biomarkers. - Recent advances in salivary biomarkers have been made for diagnosing autoimmune diseases, cardiovascular diseases, diabetes, HIV, oral cancer, caries, and periodontal diseases.

		<ul style="list-style-type: none"> - Salivary diagnostics are expected to become a reality in the near future for several diseases, with potential for chair-side tests due to their accuracy, efficacy, ease of use, and cost-effectiveness.
Preeti Kumari 2024	<p>This review paper examines the transformative role of science laboratory education in shaping students' attitudes and motivation towards science, highlighting its importance in advancing scientific education and achieving academic goals through hands-on experiences and practical skills development.</p>	<ul style="list-style-type: none"> - Science laboratory education is indispensable for improving students' understanding and perception of science, as well as their motivation to pursue careers in science and technology. - Engaging in science experiments in a laboratory setting significantly improves students' grasp of scientific facts and concepts. - Investing in laboratory facilities and experiential learning programs can enrich the educational experience and foster a lasting passion for science.
Aisha Hussein 2018	<p>This review identifies 10 promising biomarkers for tongue squamous cell carcinoma (TSCC) that have shown consistent clinical relevance in multiple publications, emphasizing the need for rigorous validation and further research to develop a specific panel for early diagnosis and prognosis.</p>	<ul style="list-style-type: none"> - The study identified 10 promising biomarkers for tongue squamous cell carcinoma (TSCC) that have been validated in at least two independent studies: IL-6, IL-8, Prolactin in liquid samples, and HIF-1α, SOX2, E-cadherin, vimentin, MALAT1, TP53, NOTCH1 in tissue biopsies. - These biomarkers are considered promising for both diagnosis and prognosis of TSCC, with potential applications in clinical decision-making such as surgical resection margins and treatment strategies. - Further research is recommended to explore the combination of these biomarkers in multi-institutional studies to improve assessment of TSCC progression.
Aliaa Al Shaar et al.	<p>This study investigates and compares variations in salivary biomarkers with their serum counterparts in recurrent aphthous stomatitis, lichen planus, and oral cancer, finding significant differences that contribute to a deeper understanding of their utility in diagnosing oral diseases and potentially improving</p>	<ul style="list-style-type: none"> - The study found statistically significant differences in salivary IgA, cortisol, and LDH levels compared to the control group, indicating their potential as diagnostic biomarkers for oral diseases. - No significant differences were observed in serum cortisol and IgA levels, suggesting saliva is a more reliable diagnostic fluid for these biomarkers. - Serum LDH levels showed significant differences in the oral cancer group,

	diagnostic and treatment strategies.	supporting its potential as a diagnostic marker.
Marco Meleti 2020	This systematic review confirms the existence of good quality evidence supporting the role of specific salivary biomarkers in diagnosing systemic diseases and malignancies, with proteins, metabolites, and RNA being the most investigated molecules, and suggests the potential for developing a "lab-on-a-chip" for saliva-based diagnosis.	<ul style="list-style-type: none"> - The systematic review confirms good quality evidence supporting the role of salivary biomarkers in diagnosing systemic diseases, particularly for lung cancer and EGFR. - A significant number of studies found statistically significant associations between salivary molecules and pathology, especially in malignant tumors. - Proteins are the most frequently investigated salivary molecules, followed by metabolites and RNA.
Elena Ferrari 2021	This systematic review provides evidence that specific salivary cytokines, such as IL-6, IL-8, and TNF- α , are present at higher concentrations in OSCC patients compared to healthy controls, supporting their potential role as biomarkers for early diagnosis of oral cancer, although further studies are needed to confirm their reliability.	<ul style="list-style-type: none"> - Salivary cytokines IL-6, IL-8, and TNF-α are present at higher concentrations in OSCC patients compared to healthy controls, indicating their potential as biomarkers for early diagnosis. - These cytokines show increasing levels with the progression of OSCC from well-differentiated to poorly differentiated lesions. - A salivary screening test based on these cytokines could be a realistic approach for diagnosing OSCC.
Ana Fernández-Olavarría 2016	This systematic review highlights the utility and clinical value of serum biomarkers in diagnosing and prognosing oral cancer, with most studies finding significant differences in patients and supporting their use despite limitations in follow-up and repeated measurements.	<ul style="list-style-type: none"> - The systematic review found that all included studies showed significant differences in patients, indicating the potential of serum biomarkers in diagnosing and prognosing oral cancer. - Biomarkers were used for determining cancerous phenotypes, predicting worse prognosis and overall survival, correlating with clinical stages, and aiding in diagnosis. - The review concludes that biomarkers are supported by clinical and scientific evidence for diagnosis and prognosis, but notes a limitation in the lack of follow-up and repeated measurements in serum.
Ilda Patrícia Ribeiro 2025	This paper provides a comprehensive review of salivaomics as a revolutionary approach for the early detection and treatment modification of oral cancer, covering its current understanding, challenges, and	<ul style="list-style-type: none"> - Salivaomics is a revolutionary approach for the early detection and treatment planning of oral cancer, offering a non-invasive and efficient method. - Despite its potential, salivaomics faces challenges such as cross-contamination and variability in saliva composition.

	future directions in diagnosis and prognosis.	- Salivaomics is considered an economically viable option for large-scale screening and personalized treatment.
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Table 5. Conclusions and Policy Recommendations

This table summarizes the key conclusions and practical recommendations from each study included in the systematic review. The "Conclusion" column brings in the most important findings with regard to the authors, i.e., diagnostic utility of salivary biomarkers, mounting evidence for salivaomics, and role of laboratory services or education interventions. The "Policy Recommendations" column incorporates practical recommendations proposed by the authors, e.g., diagnostic protocol standardization, artificial intelligence integration in laboratory platforms, point-of-care testing investments, and science education infrastructure additions. In concert, the reviews in this table summarize the translational value of the studies considered, presenting both scientific rationale and avenues for implementation for boosting health outcomes, diagnostic accuracy, and education system

Paper	Conclusion	Policy recommendations
Francesco Inchingolo 2022	The study concludes that salivary biomarker component concentration levels could be significant in detecting and diagnosing dental caries for both children and adults.	<ul style="list-style-type: none"> - Use molecular assays with salivary biomarkers for early detection and personalized management of dental caries. - Support future research with high-quality studies and sufficient follow-up to establish conclusive information on salivary biomarkers for dental caries detection and prognosis.
Adebola Adekoya 2025	<ul style="list-style-type: none"> - Medical laboratories are indispensable in healthcare delivery, particularly in LMICs, for diagnostics, disease management, and public health initiatives. - Investing in laboratory infrastructure and embracing technological advancements like AI are crucial for improving health outcomes. - Collaboration among stakeholders is vital for developing robust laboratory systems. - Recommendations are provided for policymakers, funders, and managers to effectively adopt AI and improve healthcare delivery. 	<ul style="list-style-type: none"> -Collaboration among governments, healthcare organizations, and laboratory professionals to strengthen laboratory systems. - Investing in laboratory infrastructure to improve diagnostic services. - Adoption of innovative technologies like AI to enhance laboratory capabilities. - Establishing robust regulatory frameworks for safe use of new technologies. - Infrastructure funding for advanced data centers and AI-ready systems. - Strategic investments in AI projects with clear roadmaps and scalability potential. - AI integration strategies aligned with laboratory objectives.

<p>Sarhang S Gul 2020</p>	<p>The paper concludes that while active matrix metalloproteinase-8 (aMMP8) shows promise as a biomarker for diagnosing and managing periodontal diseases, further studies are needed to improve sensitivity and specificity by combining multiple biomarkers and integrating them with risk assessment tools. The PerioSafe and ImplantSafe test kits are useful adjuncts, but future development should adhere to WHO's ASSURED criteria.</p>	<p>NA</p>
<p>Vlad Constantin 2025</p>	<ul style="list-style-type: none"> - Future research should focus on developing point-of-care diagnostic tools and integrating artificial intelligence to improve the predictive accuracy of salivary biomarkers. - The integration of advanced techniques has improved sensitivity and specificity, enabling precise and real-time diagnostics. - Lack of standardization protocols for saliva collection, storage, and biomarker validation is a significant barrier to clinical adoption. - Salivary diagnostics are evolving towards more sophisticated, non-invasive approaches, crucial for precision medicine. 	<ul style="list-style-type: none"> - Invest in research and development of point-of-care diagnostic tools and AI integration to improve predictive accuracy. - Establish standardized protocols for saliva collection, storage, and biomarker validation to ensure consistency and reliability. - Integrate salivary diagnostics into routine clinical practice. - Address regulatory and ethical considerations to ensure safe and effective implementation.
<p>Niklas Gericke 2022</p>	<ul style="list-style-type: none"> - The systematic review synthesizes research on laboratory work in secondary school science education, focusing on developing students' learning of science and learning to do science. - The review highlights the importance of guided inquiry and the challenges associated with implementing student-centred approaches. - Recommendations for future research include studying the connection between level of inquiry 	<ul style="list-style-type: none"> - Focus on the connection between level of inquiry and learning goals in laboratory work, adjusting openness to intended learning goals. - Investigate the connection between science knowledge and skills within laboratory work. - Study the issue of transfer and learning progression in laboratory work, particularly introducing control-of-variables in experiments. - Conduct further studies on assessment practices in laboratory work beyond traditional lab reports.

	and learning goals, the connection between science knowledge and skills, transfer and learning progression, and assessment practices.	
Oana Almăș 2022	<ul style="list-style-type: none"> - Association found between NLR, LMR, and PLR and periodontitis. - These ratios are emerging blood cell count inflammatory biomarkers for understanding systemic disbalances and for periodontitis prognosis and grading. - No significant association found for RDW. - Findings suggest potential for future studies on diagnostic, prognostic, and therapeutic management. 	<ul style="list-style-type: none"> - Future studies should be conducted to evaluate blood cell count inflammatory biomarkers for diagnostic, prognostic, and therapeutic management. - These biomarkers should be used to assess the impact of periodontitis on systemic health and as prognostic markers for disease evolution and treatment efficiency. - Standardized values should be employed for consistent periodontal disease diagnosis and severity grading. - Further prospective studies are needed to confirm the role of these biomarkers. - Clinicians should use these biomarkers to better classify and monitor disease progression and treatment efficiency.
Mohammad A Javid 2015	<ul style="list-style-type: none"> - Salivary diagnostic tests are expected to be available in dental offices due to their accuracy, efficacy, ease of use, and cost-effectiveness. - These tests have the potential to be used as chair-side diagnostics for various oral and systemic diseases. - Challenges include standardizing collection methods and biomarkers, developing new assays, and gaining acceptance from healthcare professionals and insurance companies. - The advent of sensitive and specific tools and guidelines is expected to make salivary diagnostics a reality in the near future. 	<ul style="list-style-type: none"> - Salivary diagnostic tests should be made available in dental offices. - Standardization and validation of salivary collection methods and biomarkers are necessary. - Cooperative agreements among government, funding agencies, academia, and the private sector are needed to develop new assays and devices. - Further studies are required to demonstrate accuracy and cost-effectiveness to gain acceptance by insurance companies and healthcare professionals.
Preeti Kumari 2024	The conclusion of the paper is that science laboratory education plays a crucial role in shaping students' attitudes and motivation towards science, making it an indispensable part of science education. Investing	<ul style="list-style-type: none"> - Address resource mobilization issues at schools by targeting budget and space constraints. - Implement a student-centered pedagogical approach with support from teachers and school management.

	<p>in laboratory facilities and experiential learning programs can enrich the educational experience. A student-centered pedagogical approach, supported by teachers and school management, is recommended to maintain laboratory resources' usability and functionality. Challenges such as budget constraints, limited space, and the need for teacher training must be addressed to enhance the effectiveness of science education. Socioeconomic background and gender may influence students' attitudes and motivation towards science education. Overall, science laboratory education is essential for improving science education quality and promoting engagement in science-oriented careers.</p>	<ul style="list-style-type: none"> - Ensure adequate support from school administration for maintaining laboratory resources. - Invest in laboratory facilities and experiential learning programs. - Address existing gaps in resources and opportunities to create an engaging learning environment.
<p>Aisha Hussein 2018 A</p>	<ul style="list-style-type: none"> - Rigorous validation of biomarkers that have shown unbiased assessment in at least two publications is a high priority. - Further research on promising biomarkers could lead to a specific panel for early diagnosis, prognosis, and personalized treatment. - The developmental path to clinically valid biomarkers is long and challenging. - Ten promising biomarkers have been identified with consistent clinical relevance. - Multi-institutional studies are needed to further validate these biomarkers. 	<ul style="list-style-type: none"> - Prioritize funding and resources for validation studies of promising biomarkers. - Emphasize the use of sound scientific and well-planned study designs, adhering to guidelines like REMARK for prognostic biomarkers. - Focus efforts on a selected set of promising biomolecules to make clinical biomarker implementation more economically viable. - Address the financial challenges in biomarker development by increasing funding or improving resource allocation.
<p>Aliaa Al Shaar et al.</p>	<ul style="list-style-type: none"> - The research contributes to a deeper understanding of the utility of salivary biomarkers in diagnosing oral diseases. - Saliva can serve as an alternative to blood samples for diagnostic purposes. 	<ul style="list-style-type: none"> - Use salivary biomarkers as a diagnostic tool for oral diseases due to their ease of collection, safety, and non-invasiveness. - Further research on salivary biomarkers could lead to advancements in patient care and cost reductions.

	<ul style="list-style-type: none"> - Saliva plays a multifaceted role in oral health, aiding in protection, digestion, and possessing antibacterial and antifungal properties. - Further exploration of salivary biomarkers can lead to advancements in patient care and disease management. - Salivary analysis is crucial for improving diagnostic and treatment strategies in dental practice. 	
Marco Meleti 2020	<p>The systematic review confirms the existence of good quality evidence supporting the role of salivary biomarkers in diagnosing systemic diseases and malignancies, such as lung cancer and EGFR. Further research is needed to improve sensitivity and specificity. The use of salivary biomarkers is gaining interest, and developing a reliable "lab-on-a-chip" is considered an attainable goal.</p>	<ul style="list-style-type: none"> - Invest in further research and development of salivary biomarkers for diagnosing systemic diseases and malignancies. - Develop and implement "lab-on-a-chip" technology for diagnosis and follow-up. - Consider the economic benefits of promoting salivary diagnostics over traditional blood-based methods. - Support future studies to improve the sensitivity and specificity of salivary analysis techniques. - Encourage the development of smaller, patient-friendly devices with affordable costs.
Elena Ferrari 2021	<ul style="list-style-type: none"> - Salivary cytokines, particularly IL-6, IL-8, and TNF-α, are present in higher concentrations in OSCC patients compared to healthy controls. - These cytokines may serve as biomarkers for the early diagnosis of oral cancer. - A salivary screening test based on these cytokines seems feasible for advancing early diagnosis. - Further studies are needed to confirm the reliability of such a test. 	NA
Ana Fernández-Olavarría 2016	<p>Biomarker use for diagnosis and prognosis is supported by clinical and scientific evidence. Monitoring protocols should be established for selected biomarkers to ensure a correct understanding of biological</p>	<ul style="list-style-type: none"> - Biomarkers are supported by clinical and scientific evidence for diagnosis and prognosis. - Monitoring protocols should be established by oral and maxillofacial surgeons to understand biological values.

	values. A limitation is the lack of follow-up and repeated measurements in serum.	
Ilda Patrícia Ribeiro 2025	<ul style="list-style-type: none"> - Salivaomics is a promising non-invasive tool for the early detection and prognosis of oral cancer. - Challenges exist in improving its effectiveness and reliability, necessitating further research. - Integration of genomics, proteomics, metabolomics, and transcriptomics can enhance its capabilities. - Salivaomics offers potential for early detection, treatment monitoring, and relapse prevention. - It is economically viable for large-scale screening and individualized treatment. 	<ul style="list-style-type: none"> - Standardize saliva collection, storage, and processing techniques to ensure reliability and consistency in research results. - Integrate genomics, proteomics, metabolomics, and transcriptomics to enhance diagnostic and therapeutic capabilities. - Conduct further large-scale studies using modern technologies like nanotechnology and AI. - Develop easy-to-use, portable, and cost-effective diagnostic tools. - Integrate salivaomics into public health screening programs.

Table 6. Qualitative Assessment of Included Studies

Here is a systematic evaluation of the methodological quality of all considered included studies. Each of the studies was assessed with a modified version of the NIH Quality Assessment Tool appropriate to this aim, considering measures of clarity of research objective, study design, population definition, methodological quality, utilization of validated biomarkers or outcomes, transparency of reporting, and control for confounding or bias. Each study was given a Good, Fair, or Poor quality rating based on these measures. The rationale column gives concise explanations for the assigned rating, highlighting strengths (e.g., PRISMA compliance, meta-analysis, systematic process) and weaknesses (e.g., no population specificity, limited statistical analysis, or no formal quality control). The assessment informs critical appraisal of strength of evidence and guides interpretation of review findings.

Paper	Study Design	Qualitative Rating	Rationale
Francesco Inchingolo (2022)	Systematic Review	Good	Clear objectives, defined populations, multiple studies analyzed; good coverage of outcomes and biomarkers, but lacks meta-analysis or risk of bias appraisal.
Adebola Adekoya (2025)	Systematic Review + Meta-analysis	Good	PRISMA-guided with meta-analytic component; broad geographical scope; detailed objectives and strong interpretive clarity.
Sarhang S. Gul (2020)	Systematic Review	Fair	Clear outcomes and biomarker analysis, but limited policy translation and minimal detail on study selection and quality control.

Vlad Constantin (2025)	Systematic Review	Fair	Review is comprehensive, but lacks population details and formal methodology evaluation; more narrative than structured.
Niklas Gericke (2022)	Systematic Review	Good	Extensive synthesis of empirical studies; clear coding and analysis; appropriate for education-focused review.
Oana Almăs (2022)	Systematic Review + Meta-analysis	Good	Well-structured with quantitative synthesis; PRISMA-compliant; clear population and biomarker reporting.
Mohammad A. Javid (2015)	Systematic Review	Fair	Broad coverage of diseases and biomarkers; lacks structured quality appraisal of included studies.
Preeti Kumari (2024)	Narrative Review	Fair	Well-articulated and thematic; lacks clear methodology, inclusion criteria, or bias handling.
Aisha A. Hussein (2018)	Systematic Review	Good	Focused scope (TSCC), strong biomarker validation criteria; limitations in follow-up discussed; supports reproducibility.
Aliaa Al Shaar et al.	Case-Control Study	Fair	Small sample size; comparative biomarker analysis strong; but lacks statistical depth and power justification.
Marco Meleti (2020)	Systematic Review (PRISMA)	Good	Large number of studies; formal quality appraisal using NIH and CEMB; detailed results reporting.
Elena Ferrari (2021)	Systematic Review (Observational)	Good	PRISMA-compliant; 27 observational studies; clear focus on salivary cytokines and clinical application.
Ana Fernández-Olavarría (2016)	Systematic Review	Fair	Broad biomarker coverage; includes varied study designs; no meta-analysis due to heterogeneity; limited follow-up discussion.
Ilda Patrícia Ribeiro (2025)	Systematic Review	Good	Comprehensive coverage of salivaomics; clear use of PRISMA 2020; appropriate study inclusion and clear interpretation.

<p>or similar populations? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?</p>														
<p>5. Was a sample size justification, power description, or variance and</p>	no	NR	NR	NR	no	no	NR	NR	NR	no	NR	NR	NR	no

effect estimates provided?														
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the time frame sufficient so that one could reasonably expect to see	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

an association between exposure and outcome if it existed?														
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of expos	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

<p>ure, or exposure measured as continuous variable)?</p>														
<p>9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>
<p>10. Was</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>	<p>NA</p>

the exposure(s) assessed more than once over time?														
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome	NA	NR	NA	NA	NA	NA	NR	NA	NA	NA	NR	NA	NA	NA

relationship between exposure(s) and outcome(s) ?														
Total scores (Yes = 1, No = 0.5, NR & NA & CD = 0)	8.5	8	8	8	8.5	8.5	8	8	8	8.5	8	8	8	8.5
Quality rating: good (14-13 point) or fair (9-12 point) or poor (8-0 points)	Fair quality	Poor quality	Poor quality	Poor quality	Fair quality	Fair quality	Poor quality	Poor quality	Poor quality	Fair quality	Poor quality	Poor quality	Poor quality	Fair quality

Ethical Considerations

No primary data were collected; ethical approval was not required. Conflicts of interest: None declared.

Discussion

Interpretation of Key Findings

This systematic review of 14 studies underscores the diagnostic and prognostic potential of laboratory biomarkers, particularly salivary biomarkers, in oral and dental diseases. Saliva emerged as a complex, non-invasive diagnostic medium, full of biomarkers including cytokines (e.g., IL-6, IL-8, TNF- α), immune cell ratios (e.g., NLR, PLR, LMR), enzymes (e.g., aMMP-8, LDH), and genetic elements (e.g., miRNA, mRNA). There were also consistent associations across conditions like dental caries (Inchingolo 2022), periodontitis (Gul 2020; Almäs 2022), OSCC (Ferrari 2021; Ribeiro 2025), TSCC (Hussein 2018), and related oral pathologies (Al Shaar et al.; Fernández-Olavarría 2016). By way of example, elevated salivary cytokines in OSCC patients are favorable for early detection, with potential screening tests having high sensitivity (Ferrari 2021). Prognostically, biomarkers like NLR/PLR grade periodontitis and predict systemic inflammation links (Almäs 2022), while salivaomics gives insight into OSCC recurrence and treatment response (Ribeiro 2025). Broader implications include medical laboratories' roles in healthcare delivery (Adekoya 2025) and laboratory education in the generation of science interest (Gericke 2022; Kumari 2024), illustrating interdisciplinary applications. Technological integrations, such as AI and nanotechnology (Constantin 2025; Adekoya 2025), enhance biomarker detection, paving the way for PoC diagnostics (Gul 2020; Javaid 2015).

These findings are in line with mounting evidence that salivary diagnostics are equally accurate as serum/tissue approaches with the additional advantages of accessibility and affordability (Meleti 2020; Javaid 2015). However, variability in associations (e.g., no association between RDW and periodontitis; Almäs 2022) suggests context-dependent usefulness.

Strengths and Limitations

Strengths include the range of study designs (e.g., meta-analyses in Almäs 2022) and international representation (e.g., multicountry studies in Inchingolo 2022, Meleti 2020), which provides a wide evidence base. Stringent appraisal was provided by using standardized tools like the NIH Quality Assessment (Table 7) and qualitative grading (Table 6), with most of the studies being graded Fair to Good.

Limitations arise from methodological heterogeneity, precluding meta-analysis, and common biases such as unreported sample size justifications or confounding adjustments (Table 7). Follow-up was short term in numerous studies (e.g., Fernández-Olavarría 2016), compromising prognostic conclusions. Saliva composition variability and standardization issues (Ribeiro 2025; Constantin 2025) complicate clinical translation. The diverse variety of themes (e.g., education-based studies) may subtract from focus but augment overall laboratory applications. Publication bias for positive associations and English-language restrictions could skew results.

Implications for Practice and Policy

Clinically, salivary biomarkers need to be integrated into routine oral health screening, especially in resource-scarce settings (Adekoya 2025). PoC devices like PerioSafe (Gul 2020) and chair-side tests (Javaid 2015) can revolutionize early detection, improving prognoses for high-burden diseases like OSCC (global incidence ~377,913 cases; Ribeiro 2025).

Policy recommendations involve standardization of saliva protocols (Constantin 2025; Javaid 2015), investment in AI-supported labs (Adekoya 2025), and multi-institutional validation (Hussein 2018; Ferrari 2021). Education policy must prioritize laboratory-based science for enhancing STEM interest (Gericke 2022; Kumari 2024). Funding to LMICs is needed to bridge infrastructural gaps (Adekoya 2025).

Future Research Directions

Future research should prioritize prospective large-scale trials with standardized methods and biomarker panels (e.g., cytokines and genetics). The application of AI for predictive modeling (Constantin 2025) and salivaomics in underresearched populations could facilitate equity. Longitudinal study designs that address follow-up and treatment effects are needed to increase prognostic evidence.

In summary, laboratory biomarkers have the potential to revolutionize oral and dental disease management, and research and deployment should be fast-tracked to take advantage of their diagnostic and prognostic value.

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