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# Diagnostic accuracy of individual salivary biomarkers measured by ELISA for periodontitis: A systematic review and meta-analysis

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## ADMINISTRATIVE INFORMATION

**Support -** This review will receive no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Review Stage at time of this submission -** Preliminary searches.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202690093

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 September 2026 and was last updated on 22 September 2026.

## INTRODUCTION

**Review question / Objective** In human participants undergoing periodontal assessment, how accurately can an individual molecular biomarker measured in saliva using enzyme-linked immunosorbent assay (ELISA) distinguish clinically diagnosed periodontitis from periodontal health or gingivitis? The index test will be an individual salivary molecular biomarker measured by ELISA. The target condition will be periodontitis, and the reference standard will be a clinical periodontal diagnosis based on the 1999 or 2018 AAP/EFP classification. The primary objective will be to obtain biomarker-specific joint estimates of sensitivity and specificity.

**Rationale** Clinical periodontal measurements and radiographic examination remain essential for diagnosing periodontitis but are time-consuming, operator-dependent, and primarily reflect accumulated tissue destruction. Saliva is non-invasive, readily available, and suitable for repeated assessment. Individual salivary biomarkers may therefore support periodontal screening or triage. However, estimates obtained using different analytical platforms may not be interchangeable. Earlier reviews combined platforms or focused mainly on the area under the receiver operating characteristic curve. An updated diagnostic-accuracy review restricted to ELISA, with biomarker-specific joint modeling of sensitivity and specificity, is needed to improve analytical comparability and identify biomarkers requiring further clinical validation.

**Condition being studied** Periodontitis is a dysbiosis-driven, host-mediated chronic inflammatory disease that causes progressive loss of periodontal attachment and alveolar bone and may ultimately lead to tooth loss. Eligible diagnoses will include chronic or aggressive periodontitis under the 1999 classification and periodontitis of any stage, grade, extent, or severity under the 2018 AAP/EFP classification. The review will assess whether individual host-

derived molecular biomarkers measured in saliva by ELISA can distinguish periodontitis from periodontal health or gingivitis.

## METHODS

**Search strategy** A preliminary search was conducted in PubMed, Embase, Scopus, LILACS, and Web of Science through June 2026, without applying a one-year date filter. The search will combine three domains: periodontitis, molecular biomarkers, and saliva. The periodontitis block will be ("periodontitis" OR "periodontal"), and the saliva block will be "saliva". The molecular-biomarker block will include: amino acid, antibody, enzyme, immunoglobulin, marker, mediator, metabolite, peptide, protein, substance, activating factor, adipocytokine, adiponectin, albumin, aminopeptidase, aminotransferase, amylase, antitrypsin, arginase, arylsulfatase, ascorbate, calcium, calgranulin, calprotectin, cathepsin, CD14, chemokine, chitinase, chondroitin, collagenase, complement C, cortisol, creatine, creatinine, cystatin, cytokine, dehydrogenase, dipeptidyl peptidase, elastase, esterase, fibronectin, gingipain, glucuronidase, glycosaminoglycan, glycosidase, growth factor, hexosaminidase, hyaluronic, hydroxydeoxyguanosine, hydroxyproline, interferon, interleukin, keratin, lactoferrin, laminin, leptin, leukotriene, lysozyme, macroglobulin, melatonin, metalloproteinase, microglobulin, myeloperoxidase, neopterin, neurokinin, nitrate, nitric oxide, nitrite, osteocalcin, osteonectin, osteopontin, osteoprotegerin, peptidase, peroxidase, phosphatase, plasminogen, prostaglandin, protease, proteinase, pyridinoline, RANKL, RANTES, resistin, stromelysin, TIMP, transferrin, urate, and visfatin. Terms within the molecular-biomarker block will be combined with OR, and the three domains will be combined with AND. Database-specific syntax will be used. No diagnostic-accuracy methodological filter will be applied during database searching. Reference lists of included studies and relevant reviews will be screened manually. ELISA will be applied as an eligibility criterion rather than as a mandatory database-search term.

After retrieval, all EndNote records will be exported to CSV and subjected to case-insensitive rule-based text mining using BSD grep in macOS Terminal. The command grep -E -i will identify records containing positive keywords, and grep -E -i -v will exclude records containing negative keywords. The complete positive-keyword set will be: accuracy, accurate, diagnostic accuracy, classification accuracy, sensitivity, true positive rate, recall, detection rate, specificity, true negative rate, threshold, cut-off, decision threshold, classification threshold, area under curve, AUC, area under the ROC curve, area under the curve, area under the curves, area under curves, areas under the curve, areas under curve, areas under the curves, areas under curves, receiver operating, ROC, receiver operating characteristic, operating characteristic, ROC curve, ROC analysis, positive predictive value, PPV, precision, positive predictive ratio, negative predictive value, NPV, negative predictive ratio, true positive, TP, #TP, true positive count, true negative, TN, #TN, true negative count, false positive, FP, #FP, false alarm, false negative, FN, #FN, missed detection, point of care, POCT, point-of-care, bedside test, chairside diagnosis, chairside test, chair-side test, rapid test, onsite test, diagnostic test, diagnostic tool, diagnostic performance, diagnostic assay, prognostic test, prognostic tool, outcome predictor, prognosis indicator, logistic regression, logit model, logistic model, logistic analysis, canonic correlation, canonical correlation, canonical analysis, odd ratio, odds ratio, OR, log odds, neuronal network, neural network, ANN, artificial neural network, support vector machine, SVM, support vector classifier, performance measure, performance metric, evaluation metric, classifier performance, predictive model, prediction model, forecasting model, classifier model, high fidelity, precise, predictive ability, forecast, estimation, regression, regression analysis, linear regression, multivariate regression, discriminant, discriminant function, discriminant analysis, cluster, clustering, unsupervised classification, cluster analysis, cluster assignment, clustering method, variance, variability, standard deviation, fluctuation, and dispersion. The negative-keyword set will be: dog, cat, animal, mouse, rat, vitro, monkey, pig, and rabbit. Before formal use, a random sample of 500 records will be screened both manually and by the text-mining procedure. Its sensitivity and specificity will be calculated with two-sided Clopper–Pearson exact 95% confidence intervals. Records retained after text mining will undergo independent full-text eligibility assessment by two reviewers.

**Participant or population** Human participants undergoing periodontal assessment will be eligible. The review will include clinically diagnosed periodontitis cases and controls who are periodontally healthy or have gingivitis. Participants with explicitly diagnosed systemic or syndromic medical conditions, pregnancy, or alcoholism will be excluded. Animal and in-vitro studies will also be excluded.

**Intervention** The index test will be an individual molecular biomarker measured in saliva using ELISA and intended to distinguish periodontitis from non-periodontitis. Combined biomarker panels, bacterial biomarkers, and biomarkers measured in non-salivary specimens will be excluded. No restriction will be imposed on stimulated versus unstimulated saliva.

**Comparator** The comparator will be participants classified as periodontally healthy or having gingivitis according to the original study definitions. The reference standard will be a clinical periodontal diagnosis based on the 1999 or 2018 AAP/EFP classification, including clinical attachment loss and radiographic bone loss. No restriction will be imposed on diagnostic criteria or classification thresholds; diagnoses will be accepted as defined by the original investigators.

**Study designs to be included** Cross-sectional, case-control, and cohort diagnostic-accuracy studies evaluating a single salivary molecular biomarker measured by ELISA will be included if they report a complete 2 × 2 table or sufficient data to reconstruct true-positive, false-positive, true-negative, and false-negative counts.

**Eligibility criteria** Original English-language human studies will be eligible if they evaluate a single salivary molecular biomarker measured by ELISA for detecting clinically diagnosed periodontitis and provide sufficient diagnostic-accuracy data. Diagnoses under the 1999 or 2018 AAP/EFP classification will be accepted as defined by the original investigators, without restriction on classification thresholds. Studies will be excluded if they involve systemic disease, alcoholism, or pregnancy; evaluate gingivitis, peri-implantitis, mixed gingivitis-periodontitis groups, or another target condition; assess bacterial biomarkers, genetic or epidemiological associations, disease progression, or treatment response; use non-salivary specimens or multi-biomarker models; lack clear clinical diagnostic criteria; or provide insufficient data. Theses, dissertations, reviews, letters, opinion articles, book chapters, short communications, conference abstracts, and patents will be excluded. No publication-year restriction will be imposed.

**Information sources** PubMed, Embase, Scopus, LILACS, and Web of Science will be searched. Reference lists of included studies and relevant reviews will be screened manually. Full texts and supplementary materials will be examined. When diagnostic-accuracy, assay, threshold, specimen-handling, or participant information is missing or unclear, it will be derived from the report when possible and corresponding authors will be contacted when feasible.

**Main outcome(s)** The primary outcomes will be pooled biomarker-specific sensitivity and specificity for detecting periodontitis . For each biomarker represented by at least three eligible ELISA studies, pooled sensitivity and specificity with 95% confidence intervals will be jointly estimated using a bivariate random-effects model.

**Additional outcome(s)** Additional outcomes will include summary receiver operating characteristic curves, 95% confidence and prediction regions, between-study heterogeneity, and Deeks' funnel-plot asymmetry test when enough studies are available. Potential sources of heterogeneity will be explored through biomarker-specific bivariate meta-regression using diagnostic threshold, geographic region, age, sex, smoking status, and detection platform as study-level covariates when data permit.

**Data management** Records will be imported into EndNote 21, deduplicated, and exported to CSV for rule-based text mining using positive and negative keywords. The filtering procedure will be validated against manual screening of a random sample of 500 records. Two reviewers, Han and Lin, will independently assess the retained full-text articles. Disagreements will be resolved through discussion; Wang will adjudicate unresolved cases. Data will be collected from full texts and supplements using a standardized form developed in the Notion database. Extracted items will include 2 × 2 contingency-table data, participant characteristics, index-test characteristics, saliva-sampling methods, ELISA detection details, diagnostic thresholds, and reference-standard definitions. Missing or unclear data will be derived when possible, cross-checked against the original reports, documented, and queried with study authors when feasible.

**Quality assessment / Risk of bias analysis** Two reviewers will independently assess risk of bias and applicability using QUADAS-2. Risk of bias will be evaluated in four domains: patient selection, index test, reference standard, and flow and timing. Applicability concerns will be evaluated for patient selection, index test, and reference standard. Signaling questions will support judgments of low, high, or unclear risk. Disagreements will be resolved by discussion; Wang will adjudicate if consensus cannot be reached.

**Strategy of data synthesis** Quantitative synthesis will be performed separately for each biomarker reported by at least three eligible ELISA studies with sufficient 2 × 2 data. All eligible studies will be included regardless of diagnostic threshold. Sensitivity and specificity will be jointly estimated using a bivariate random-effects model, which accounts for their correlation and between-study heterogeneity. The generalized linear mixed model will be fitted using the metadta package in Stata version 18.0. Results will include pooled sensitivity and specificity with 95% confidence intervals, coupled forest plots, and summary receiver operating characteristic curves with confidence and prediction regions. Biomarkers unsuitable for quantitative pooling will be summarized narratively. Deeks' funnel-plot asymmetry test will be used to explore small-study effects when sufficient studies are available.

**Subgroup analysis** Biomarker-specific bivariate meta-regression will be fitted using metadta in Stata version 18.0. The bivariate random-effects model will be extended using study-level covariates. Methodological covariates will include diagnostic threshold and detection platform. Demographic and clinical covariates will include geographic region, age, sex, and smoking status. The association of each covariate with logit sensitivity and logit specificity will be evaluated separately when the number of studies and completeness of reporting permit meaningful estimation.

**Sensitivity analysis** No formal sensitivity analysis is planned. The absence of a sensitivity analysis will be reported transparently.

**Language restriction** Yes. Eligibility will be restricted to original research articles published in English.

**Country(ies) involved** Taiwan.

**Keywords** saliva; biomarker; periodontitis; ELISA; diagnostic accuracy; sensitivity; specificity; meta-analysis.

**Dissemination plans** The completed review will be submitted to the Journal of Clinical Periodontology and may be presented at academic or professional meetings. Reporting will follow PRISMA-DTA and will include the eligibility criteria, complete search methods, study selection, risk-of-bias assessment, data extraction, and biomarker-specific diagnostic-accuracy synthesis.

**Contributions of each author**

Author 1 - Yu Chen Han - Conceptualization, methodology, literature search, study selection, data extraction, data analysis, visualization, and drafting of the manuscript. Coordinated the project and revised the manuscript.
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Author 2 - Chen Ying Wang - Contributed to conceptualization, clinical interpretation, methodology, supervision, and critical revision of the manuscript. Reviewed the study findings and approved the final manuscript.
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Author 3 - Yu-Kang Tu - Methodology, statistical analysis and interpretation, validation of the meta-analytic methods, and critical review and revision of the manuscript.
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