INPLASY

Oral-Fluid Inflammatory and Oxidative-Stress Biomarkers for Peri-implantitis in Asian Adults: A Systematic Review and Stratified Random-Effects Meta-analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 May 2026 and was last updated on 26 May 2026.

INTRODUCTION

Review question / Objective Population (P): Asian adults with peri-implantitis, peri-implant mucositis, or healthy dental implants.
Intervention/Exposure (I): Measurement of inflammatory cytokines (IL-1β, IL-6, TNF-α) and oxidative-stress/immune-regulatory marker (SIRT1) in oral fluids (peri-implant crevicular fluid [PICF] and saliva).
Comparator (C): Healthy peri-implant controls or Asian adults without peri-implantitis.
Outcomes (O): Differences in biomarker concentrations; diagnostic performance of SIRT1 (AUC, sensitivity, specificity); subgroup effects by specimen type, diagnostic criteria, and analysis unit; heterogeneity and publication bias.
Study design (S): Observational clinical studies (cross-sectional, case–control, cohort).
Review Objective: To conduct a systematic review and stratified random-effects meta-analysis of oral-fluid inflammatory and oxidative-stress biomarkers for peri-implantitis in Asian adults, comparing biomarker levels between peri-implantitis patients and healthy controls, and evaluating their potential as adjunctive diagnostic markers.

Condition being studied Peri-implantitis is a common inflammatory disease affecting the tissues around dental implants, triggered by bacterial biofilm accumulation. It is characterized by soft-tissue inflammation, bleeding on probing, suppuration, progressive peri-implant bone loss, and increased probing depth, which can ultimately lead to implant failure. Unlike reversible peri-implant mucositis, peri-implantitis causes irreversible destruction of the supporting bone. Current clinical diagnosis mainly relies on late-stage signs (clinical indices and radiographs), making early detection challenging. Therefore, identifying minimally invasive oral-fluid biomarkers to reflect disease activity and support early diagnosis is clinically important.

METHODS

Participant or population This review focuses on Asian adults (aged ≥18 years) with dental implants, including three groups:
Patients with peri-implantitis: Asian adults diagnosed with peri-implantitis using established criteria (e.g., 2017 World Workshop consensus or earlier definitions).
Patients with peri-implant mucositis: Asian adults with reversible inflammation of peri-implant soft tissues, without bone loss.
Healthy controls: Asian adults with clinically healthy dental implants, no signs of peri-implant inflammation or bone loss.
Excluded populations: Children/adolescents, non-Asian ethnicities, individuals with systemic conditions (e.g., uncontrolled diabetes, autoimmune diseases) that may confound biomarker levels, and those with a history of recent oral surgery or antibiotic use.

Intervention The intervention of interest is the measurement of inflammatory and oxidative-stress biomarkers in oral fluids (peri-implant crevicular fluid [PICF] and whole saliva) from participants with dental implants. The evaluated biomarkers include:
Inflammatory cytokines: Interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α);
Oxidative-stress/immune-regulatory marker: Sirtuin-1 (SIRT1).
Assay methods for biomarker quantification include ELISA and multiplex immunoassays. The intervention is minimally invasive, focusing on non-surgical oral fluid sampling to assess peri-implant disease status, rather than therapeutic interventions.

Comparator The comparator group consists of Asian adults with clinically healthy dental implants (no signs of peri-implantitis or peri-implant mucositis, with normal probing depths, no bleeding on probing, and no radiographic bone loss around implants). Their oral-fluid biomarker levels serve as the reference to compare against participants with peri-implantitis.

Study designs to be included This review will include observational clinical study designs that compare oral-fluid biomarker levels between Asian adults with peri-implantitis and healthy implant controls. Eligible designs are:Cross-sectional studies: Measuring biomarker concentrations and clinical status at a single time point.Case–control studies: Comparing biomarker levels in cases (peri-implantitis) versus matched or unmatched healthy controls.Cohort studies (prospective/retrospective): Evaluating baseline biomarkers in relation to subsequent peri-implantitis development or progression.Excluded designs: In vitro.

Eligibility criteria Inclusion criteria
Full-text articles published in English or Chinese, with no restriction on publication date (up to August 2025).
Studies focusing exclusively on human Asian adult populations (≥18 years) with dental implants.
Original data reporting quantitative concentrations of target biomarkers (IL-1β, IL-6, TNF-α, SIRT1) in peri-implant crevicular fluid (PICF) or saliva.
Studies providing clear diagnostic criteria for peri-implantitis, peri-implant mucositis, or healthy implant status.
Sufficient data to calculate effect sizes (e.g., mean ± standard deviation, sample size) or diagnostic performance metrics (AUC, sensitivity, specificity).
Exclusion criteria
In vitro, animal, or laboratory-based experimental studies.
Review articles, meta-analyses, case reports, letters, editorials, conference abstracts, or unpublished data.
Studies lacking separate control groups (healthy implants) or failing to report raw biomarker values.
Studies enrolling participants with systemic diseases (e.g., uncontrolled diabetes, autoimmune disorders), severe periodontitis, or recent oral surgery/antibiotic use that may confound biomarker levels.
Non-Asian populations, participants younger than 18 years, or edentulous individuals without dental implants.

Information sources This systematic review will search five electronic databases from their inception to August 2025, without language restrictions (English and Chinese):
PubMed (MEDLINE): For biomedical and dental literature.
Embase: For pharmacological and oral health research.
Web of Science Core Collection: For comprehensive interdisciplinary coverage.
Cochrane Library: For clinical evidence and systematic reviews.
China National Knowledge Infrastructure (CNKI): For Chinese-language dental and clinical studies.
Additional supplementary sources:
Manual screening: Reference lists of all included studies and relevant reviews to identify missed eligible articles.
Grey literature: Conference abstracts, theses, and unpublished data will not be included due to insufficient extractable data.

Author contact: No formal contact with authors will be performed, as only published data is analyzed.

Main outcome(s) Primary outcomes
Differences in oral-fluid biomarker concentrations between participants with peri-implantitis and healthy implant controls.
Biomarkers: IL-1β, IL-6, TNF-α (inflammatory cytokines), and SIRT1 (oxidative-stress/immune-regulatory marker).
Specimens: peri-implant crevicular fluid (PICF) and whole saliva.
Effect measure: Standardized mean difference (SMD, Hedges' g) with 95% confidence intervals (CIs), calculated from reported means, standard deviations, and sample sizes.
Timing: Single time-point measurements as reported in included cross-sectional, case–control, or cohort studies.
Diagnostic performance of SIRT1 for peri-implantitis.
Effect measures: Pooled area under the curve (AUC) (logit scale, random-effects model), sensitivity, and specificity with 95% CIs.
Timing: Baseline diagnostic assessment at the time of peri-implantitis diagnosis.
Secondary outcomes
Subgroup analyses of biomarker differences by specimen type (PICF vs saliva), analysis unit (patient-level vs implant-level), and diagnostic criteria (2017 World Workshop consensus vs non-consensus definitions).
Meta-regression analyses to explore potential moderators of effect sizes: biomarker class (inflammatory vs oxidative-stress), assay method (ELISA vs multiplex), sample size, and publication year.
Heterogeneity assessment: Quantified using the I^2 statistic, Cochran's Q test, and τ^2 estimates.
Publication bias: Evaluated via funnel plots, Egger's regression test, and trim-and-fill analysis (where applicable).

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the 13 included primary observational studies (cross-sectional, case-control, cohort) were evaluated using two standardized critical appraisal tools, tailored to study design:
Joanna Briggs Institute (JBI) Critical Appraisal Checklist: Applied for prevalence/cross-sectional studies (the majority of included work).
Newcastle–Ottawa Scale (NOS): Used for case-control studies among the included literature.
1. Scoring and Risk Classification
Studies were categorized into three risk levels based on total scores:
Low risk: ≥6 points
Moderate risk: 4–5 points
High risk: ≤3 points
2. Visualization of Risk of Bias
A risk-of-bias summary plot was generated using the robvis package in R software, to visually present the risk distribution across included studies.
3. Overall Risk Profile of Included Studies
Most included studies were rated low risk of bias.
A small number of earlier studies (e.g., Zhang 2005; Yaghobee 2013, 2014; Chen 2020) were classified as moderate risk, primarily due to small sample sizes and implant-level rather than patient-level analysis.

Strategy of data synthesis Data synthesis will be performed using R software (version 4.3.2) with the metafor and meta packages. A random-effects model will be used for all pooled analyses to account for between-study heterogeneity.
1. Continuous outcomes (IL-1β, IL-6, TNF-α concentrations)
Effect measure: Standardized mean difference (SMD, Hedges' g) with 95% confidence intervals (CIs), calculated from raw means, standard deviations, and sample sizes.
No log-transformation will be applied to cytokine concentrations before pooling.
Between-study heterogeneity will be assessed using the I^2 statistic, Cochran's Q test, and τ^2 estimates; 95% prediction intervals will be reported to reflect true effect dispersion.
2. Diagnostic outcome (SIRT1 performance)
Reported AUC values will be pooled on the logit scale using a random-effects model.
Pooled sensitivity and specificity will be summarized with 95% CIs.
3. Subgroup analysis
Stratified by: specimen type (PICF vs saliva), analysis unit (patient vs implant), and diagnostic criteria (2017 consensus vs non-consensus).
4. Meta-regression
To explore moderators: biomarker class, assay method, sample size, and publication year.
5. Sensitivity analysis
Leave-one-out analysis to test the stability of pooled results.
Exclusion of small studies (total sample size <40) and outlier studies with the largest SMD.
6. Publication bias
Assessed via funnel plots and Egger's regression test.
If ≥10 studies, trim-and-fill, PET-PEESE, and selection models will be applied.
7. Statistical significance
A two-tailed p-value < 0.05 will be considered statistically significant.

Subgroup analysis Subgroup analyses were performed on the three inflammatory biomarkers (IL-1β、IL-6、TNF-α) to explore whether the pooled effects varied by specimen type, analysis unit, and diagnostic criteria.
1. By specimen type
PICF: Significantly elevated levels, SMD = 2.46 (95% CI: 2.07–2.85), low heterogeneity.
Saliva: Significantly elevated levels, SMD = 3.06 (95% CI: 2.61–3.50), low heterogeneity.
Conclusion: Both PICF and saliva yielded consistent and robust results.
2. By analysis unit
Implant-level: SMD = 2.62 (95% CI: 2.35–2.90).
Patient-level: SMD = 2.45 (95% CI: 1.93–2.97).
Conclusion: Findings were similar regardless of implant-level or patient-level analysis.
3. By diagnostic criteria
Non-2017 criteria: SMD = 2.70 (95% CI: 2.36–3.04), robust effect.
2017 consensus criteria: SMD = 2.43 (95% CI: −4.76 to 9.62), wide CI due to limited sample size.
Conclusion: Results were stable across different diagnostic definitions.
4. Overall finding
Subgroup analyses confirmed the robustness of the main results.
The elevated inflammatory biomarker levels in peri-implantitis were consistent across specimen type, analysis unit, and diagnostic criteria.Subgroup analyses will stratify pooled biomarker effects by specimen type (peri-implant crevicular fluid vs saliva), analysis unit (patient-level vs implant-level), and diagnostic criteria (2017 World Workshop consensus vs non-consensus definitions). Random-effects models will compare effect sizes across subgroups, with 95% CIs and I^2 to assess subgroup-specific heterogeneity.

Sensitivity analysis The study conducted leave-one-out sensitivity analysis and influence diagnostics to test the robustness of the pooled effect sizes for inflammatory biomarkers (IL-1β, IL-6, TNF-α) and to identify studies driving heterogeneity.
1. Leave-one-out analysis
Each included study was sequentially removed one at a time, and the meta-analysis was re-run.
The pooled SMDs and 95% CIs remained stable and statistically significant after omitting any single study.
No individual study altered the overall conclusion of significantly elevated inflammatory markers in peri-implantitis.
2. Influence diagnostics (Baujat plots & influence statistics)
A few studies (Chen 2020, Wang 2022) contributed relatively more to between-study heterogeneity.
No extreme outliers were detected; the overall pooled estimates were not unduly driven by any single study.
3. Overall finding
Sensitivity analyses confirmed that the main results were robust, not sensitive to the exclusion of individual studies, and unaffected by minor sources of heterogeneitySensitivity analysis will use leave-one-out to test pooled result stability by sequentially omitting one study at a time. Additional sensitivity checks will exclude small studies (total sample size <40) and the study with the largest effect size for each biomarker, re-estimating SMD and heterogeneity to confirm robustness.

Country(ies) involved China.

Keywords peri-implantitis; peri-implant crevicular fluid; saliva; biomarkers.

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