

Immune-inflammatory Modulation by Non-surgical Therapies in Peri-implantitis

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ABSTRACT

To evaluate the effects of non-surgical treatment on inflammatory factor levels in patients with peri-implantitis (PI).

PubMed, Web of Science, ScienceDirect, China National Knowledge Infrastructure, and Wanfang were searched through March 2026 for randomized controlled trials of non-surgical therapy for PI. Outcomes included interleukin 1 β (IL-1 β), interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), and matrix metalloproteinase 8 (MMP-8). Meta-analysis was performed using RevMan 5.3.

Fourteen trials were included. At 3 months, adjunctive non-surgical treatment produced greater reductions than control treatment in gingival crevicular fluid IL-1 β (SMD, -0.78; 95% CI, -1.29 to -0.26), IL-6 (SMD, -1.49; 95% CI, -2.07 to -0.91), and TNF- α (SMD, -1.84; 95% CI, -3.05 to -0.63), but not MMP-8 (SMD, 0.08; 95% CI, -1.33 to 1.50). At 6 months, no between-group difference was observed for IL-1 β (SMD, -0.18; 95% CI, -0.61 to 0.25). PDT-based regimens reduced IL-1 β and TNF- α more than controls at 3 months, whereas laser-based regimens showed no clear advantage. Non-smokers showed greater IL-1 β improvement than smokers. Sensitivity analyses supported the IL-1 β , IL-6, and TNF- α findings, but the MMP-8 result was unstable. GRADE evidence quality was moderate for IL-1 β , IL-6, and TNF- α and low for MMP-8.

Non-surgical treatment may reduce gingival crevicular fluid IL-1 β , IL-6, and TNF- α levels in the short term. Non-smokers may respond better than smokers, and PDT-based regimens may be more effective than laser therapy; however, benefits were not sustained at 6 months.

Keywords: Cytokines; Gingival crevicular fluid; Laser Therapy peri-implantitis; Photochemotherapy

INTRODUCTION

Peri-implantitis (PI) represents a major challenge in

dental implantology, with a prevalence as high as 47%.¹ Without timely and standardized intervention, PI can lead to a poor prognosis for implant-supported restorations and may necessitate implant removal in severe cases, making it a leading complication associated with implant failure. Tissue damage induced by PI activates innate immune cells, including macrophages, dendritic cells, mast cells, and

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neutrophils, which mediate inflammatory responses. The massive release of proinflammatory cytokines, including interleukin 1 β (IL-1 β) and interleukin 6 (IL-6), enables inflammation to invade alveolar bone-supporting tissues, inducing osteolysis, damaging implant-bone interface stability, and causing implant loosening and loss. Accordingly, inflammation is a core factor driving the occurrence and progression of PI.² Because of the unique peri-implant anatomy, local inflammation tends to persist and recur, making complete eradication difficult and necessitating timely intervention.³ Anaerobic polymicrobial infection is recognized as a core etiology of PI.⁴ Therefore, anti-infective and anti-inflammatory therapies are essential to constrain disease progression and improve implant survival.

Currently, minimally invasive non-surgical approaches, including mechanical debridement, photodynamic therapy (PDT), laser therapy, and local irrigation, are prioritized for PI treatment because of their safety and accessibility. Mechanical debridement is regarded as first-line therapy; however, it cannot completely eliminate biofilms from irregular implant surfaces, thereby limiting therapeutic efficacy. Furthermore, the anti-inflammatory effects of laser therapy and PDT remain controversial. Some studies have found that PDT can reduce IL-1 β .⁵ However, other trials have found no distinct between-group differences in cytokine modulation.⁶

Although previous systematic reviews have summarized non-surgical PI treatments,⁷ few have quantitatively analyzed inflammatory cytokines, such as IL-1 β and IL-6, in gingival crevicular fluid. Accordingly, this meta-analysis systematically evaluated the effects of non-surgical interventions on inflammatory cytokine levels and compared the magnitude of their anti-inflammatory effects. This study aimed to clarify the clinical value of non-surgical therapy for PI and provide evidence for optimizing clinical treatment regimens.

MATERIALS AND METHODS

Study Protocol

All authors approved the protocol, which was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Literature Search Strategy

Searches were conducted in China National Knowledge Infrastructure (CNKI), Wanfang, PubMed, Web of Science, and ScienceDirect from January 1997 through March 2026. A combination of subject headings and free-text terms was used. Reference lists of included studies were manually searched, and ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) were searched to identify completed but unpublished relevant clinical trials. English search terms included peri-implant diseases, peri-implantitis, PI, non-surgical therapies, laser, diode laser, Er:YAG laser, photodynamic therapy, IL-6, IL-1 β , TNF- α , MMP-8, and inflammation. The search strategies for each database were as follows:

PubMed: (peri-implant diseases[Title/Abstract] OR peri-implantitis[Title/Abstract] OR PI[Title/Abstract]) AND (non-surgical therapies[Title/Abstract] OR photodynamic therapy[Title/Abstract] OR PDT[Title/Abstract] OR laser[Title/Abstract] OR diode laser[Title/Abstract] OR Er:YAG laser[Title/Abstract]) AND (inflammation[Title/Abstract] OR TNF- α [Title/Abstract] OR IL-1 β [Title/Abstract] OR IL-6[Title/Abstract] OR MMP-8[Title/Abstract]).

Web of Science: TS=(peri-implant diseases OR peri-implantitis OR PI) AND TS=(non-surgical therapies OR photodynamic therapy OR PDT OR laser OR diode laser OR Er:YAG laser) AND TS=(inflammation OR TNF- α OR IL-1 β OR IL-6 OR MMP-8).

ScienceDirect: peri-implant diseases*:ti OR peri-implantitis*:ti OR PI*:ti AND non-surgical therapies*:ti OR photodynamic therapy*:ti OR PDT*:ti OR laser*:ti OR diode laser*:ti OR Er:YAG laser*:ti AND IL-6*:ti OR TNF- α *:ti OR IL-1 β *:ti OR MMP-8*:ti OR inflammation*:ti.

CNKI: (Topic: peri-implant diseases OR Topic: peri-implantitis OR Topic: PI) AND (Topic: non-surgical therapies OR Topic: photodynamic therapy OR Topic: PDT OR Topic: laser OR Topic: diode laser OR Topic: Er:YAG laser) AND (Topic: inflammation OR Topic: TNF- α OR Topic: IL-1 β OR Topic: IL-6 OR Topic: MMP-8).

Wanfang: Title/Keyword: peri-implant diseases OR Title/Keyword: peri-implantitis OR Title/Keyword: PI AND Title/Keyword: non-surgical therapies OR Title/Keyword: photodynamic therapy OR Title/Keyword: PDT OR Title/Keyword: laser OR Title/Keyword: diode laser OR Title/Keyword: Er:YAG

Non-surgical Therapy Effects on Inflammation in Peri-implantitis

laser AND Title/Keyword: inflammation OR Title/Keyword: TNF- α OR Title/Keyword: IL-1 β OR Title/Keyword: IL-6 OR Title/Keyword: MMP-8.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) participants were adults who had undergone implant rehabilitation and were diagnosed with PI; (2) the study was a published randomized controlled trial (RCT); (3) both groups received non-surgical treatment, with the control group receiving conventional non-surgical treatment, including mechanical debridement, subgingival scaling, irrigation, ultrasonic scaling, air-abrasive debridement, or local or systemic antibiotics, and the observation group receiving an adjunctive non-surgical treatment, such as laser therapy, PDT, or probiotics; (4) at least 1 outcome was reported, including tumor necrosis factor α (TNF- α), matrix metalloproteinase 8 (MMP-8), IL-1 β , or IL-6; (5) the study was published in a core journal; and (6) follow-up was 3 months or longer.

Exclusion criteria were as follows: (1) patients had severe systemic disease, uncontrolled diabetes, immune disorders, malignant tumors, or other comorbidities; (2) participants were children; (3) the publication was a conference abstract, review, systematic analysis, animal experiment, case report, or master's thesis; (4) the study involved surgical intervention, such as flap surgery, bone grafting, or resective surgery; (5) the study had poor methodological quality, unclear data, or data that could not be extracted; (6) the publication was not in Chinese or English; (7) the treatment course was unclear; (8) patients had untreated periodontal disease before implant surgery; or (9) participants had taken or were permitted to take antibiotics within 6 months before study initiation.

Literature Screening and Data Extraction

Two reviewers independently screened the literature and extracted data, with cross-checking. Disagreements were resolved by consultation with a third reviewer. When possible, missing data were obtained by contacting the original authors. Extracted data included the first author, publication year, sample size, age, interventions, follow-up duration, and outcome measures.

Quality Assessment

Two reviewers independently assessed the risk of bias in the included studies using the Cochrane Risk of Bias Tool for randomized controlled trials. Evidence

quality was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Statistical Methods

Meta-analyses were performed using RevMan 5.3 and SPSS AU software. Continuous data were expressed as mean differences (MDs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs). Heterogeneity was evaluated using the χ^2 test and the I^2 statistic. If $I^2 \leq 50\%$ and $p \geq .10$, a fixed-effects model was used. Otherwise, a random-effects model was applied, and sensitivity analysis was performed by sequentially omitting individual studies to assess the robustness of the results. The significance level, α , was set at 0.05.

A random-effects model was used if $I^2 > 50\%$ in any subgroup; otherwise, a fixed-effects model was adopted when $I^2 < 50\%$ across all subgroups. For continuous data presented only in figures without raw data, values were extracted using WebPlotDigitizer. For outcomes reported in inconsistent units, SMDs were used for pooled analysis. For data reported as medians (Q1–Q3), the Scenario 2 online conversion tool provided by Hong Kong Baptist University was used to convert values to means (M) and standard deviations (SDs). For each outcome, all eligible studies were first included in an overall pooled analysis to evaluate the general effect of non-surgical treatment in patients with PI. Subgroup analyses were then performed for outcomes with sufficient data to explore potential sources of heterogeneity.

Subgroup Analysis

Smoking status: studies were grouped according to whether patients smoked.

Type of non-surgical treatment: studies were grouped according to the non-surgical modality, such as PDT or laser therapy.

If fewer than 2 studies reported stratified data for an outcome, subgroup analysis was not performed because of insufficient statistical power, and only the overall pooled effect was reported.

RESULTS

Literature Search and Screening

A total of 781 articles were initially retrieved through database searches. After screening according to

the predefined inclusion and exclusion criteria, 14 studies were included in the meta-analysis. The study selection flowchart is shown in Figure 1.

Basic Characteristics of Included Studies

The basic characteristics of the included studies are summarized in Table 1.⁶⁻¹⁹

Risk-of-bias Assessment

A total of 14 randomized controlled trials were included. Methodological quality was assessed using the Cochrane Risk of Bias Tool. Most studies had a low or unclear risk of bias for random sequence generation and allocation concealment. Performance bias, related to blinding of participants and personnel, was the main weakness, with 2 trials at low risk, 1 at unclear risk, and 11 at high risk. All trials were at low risk of bias for blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Overall, methodological quality was good for objective outcomes, but performance bias was high because of the nature of PDT and laser interventions. Risk-of-bias assessments are shown in Figures 2 and 3.

IL-1 β

Eleven studies reported IL-1 β data for patients with PI. Substantial heterogeneity was observed across studies ($I^2>50\%$; $p<0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group had a significantly greater reduction in IL-1 β levels than the control group (SMD, -0.78 ; 95% CI, -1.29 to -0.26 ; $p=0.003$). At the 6-month follow-up, no significant between-group difference was observed in IL-1 β improvement (SMD, -0.18 ; 95% CI, -0.61 to 0.25 ; $p=0.42$). Detailed data are shown in Figure 4.

Subgroup Analysis by Smoking Status

Stratified analysis by smoking status showed substantial heterogeneity across studies ($I^2>50\%$; $p<0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group had a significantly greater reduction in IL-1 β levels than the control group among non-smoking patients (SMD, -1.18 ; 95% CI, -1.98 to -0.39 ; $p=0.004$). Among smoking patients, no significant between-group difference was observed in IL-1 β reduction (SMD, -0.54 ; 95% CI, -1.20 to 0.11 ; $p=0.10$), as shown in Figure 5.

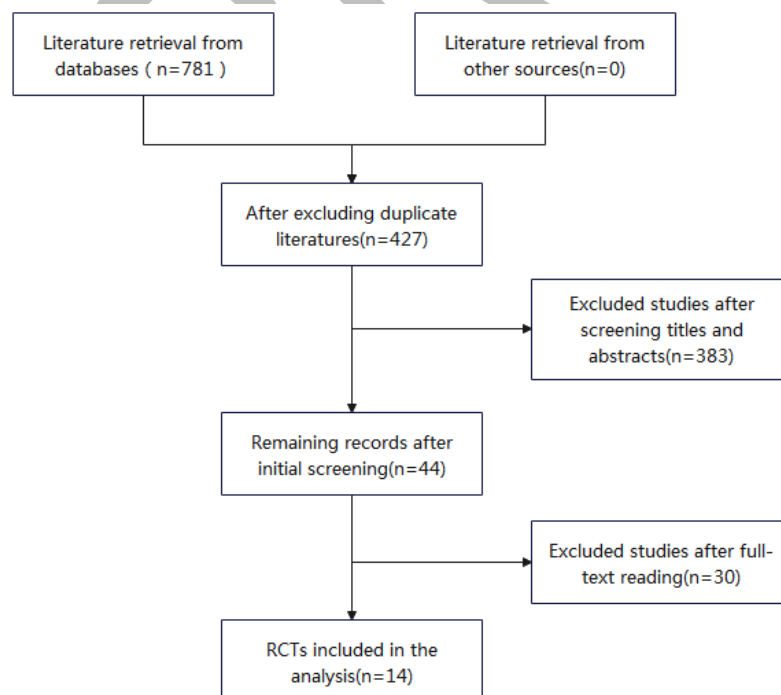


Figure 1. Literature Retrieval Flowchart.

Non-surgical Therapy Effects on Inflammation in Peri-implantitis

Table 1. Characteristics of patients included in the study

Reference	Age (T/C)	Intervention, T	Intervention, C	Sample size, T/C	Follow-up, months	Outcome measures
Ahmed AR 2023 ⁷	35.05±3.4	PDT+NSD	NSD	32/32	3, 6	IL-1β, TNF-α
Al-Khureif AA 2020 ⁸	T: 46.6 (41–55) C: 49.8 (40–58)	PDT+MD	LAT+MD	T: 25 C: 25	3, 6, 12	IL-1β
Altinda D 2023 ⁹	51.40±10.15	Diode laser+mechanical debridement with titanium curettes and airflow	Mechanical debridement with titanium curettes and airflow	T: 20 C: 20	3	IL-1β
Bassetti M 2013 ⁶	T: 59 (27–78) C: 57 (29–75)	PDT+MD	LDD+MD	T: 20 C: 20	3, 6, 9, 12	IL-1β, MMP-8
Erduran NE 2024 ¹⁰	T: 56.88±7.87 C: 56.36±12.59	Diode laser+MD	MD	T: 19 C: 18	3, 6	IL-1β
Nedumaran N 2025 ¹¹	T: 42.06±6.04 C: 43.56±7.12	PDT+MD	MD	T: 30 C: 15	3	IL-6
Roccuzzo A 2022 ¹²	T: 67.3±12.2 C: 61.0±13.2	Diode laser+MD	MD	T: 12 C: 13	3, 6	IL-1β, MMP-8
Reyila Ai-ke-lan-mu 2025 ¹³	T: 52.12±5.89 C: 51.86±6.40	PDT+MD	MD	T: 35 C: 35	3, 6	IL-1β, IL-6, TNF-α
Hu MN 2019 ¹⁴	T: 46.57±8.13 C: 47.28±7.04	Basic periodontal treatment+BioGaia probiotic drops	Basic periodontal treatment	T: 43 C: 43	3	IL-1β, TNF-α, MMP-8, IL-6
Li SN 2023 ¹⁵	T: 46.29±6.31 C: 45.87±5.53	Semiconductor laser+initial periodontal therapy	Initial periodontal therapy	T: 41 C: 41	3	TNF-α
Liu Y 2023 ¹⁶	T: 52.51±13.03 C: 50.10±13.47	Implant polishing+Er:YAG laser therapy	Implant polishing therapy	T: 35 C: 20	3	IL-1β, MMP-8
Liu XX 2018 ¹⁷	51.69±9.33	PDT+MD	MD	T: 14 C: 14	3	IL-1β, TNF-α
Tian XM 2023 ¹⁸	T: 40.3±4.2 C: 40.0±4.0	Implant polishing and subgingival scraping+Er,Cr:YSGG laser	Implant polishing and subgingival scraping	T: 42 C: 42	3	IL-1β, MMP-8, IL-6
Zhao YJ 2019 ¹⁹	47.1±7.6	Low-level laser+initial periodontal therapy	Initial periodontal therapy	T: 19 C: 19	3	IL-1β

control; Er,Cr:YSGG: erbium, chromium-doped yttrium-scandium-gallium-garnet; Er:YAG: erbium-doped yttrium-aluminum-garnet; IL-1β: interleukin 1β; IL-6: interleukin 6; LAT: local antimicrobial therapy; LDD: local drug delivery; MD: mechanical debridement; MMP-8: matrix metalloproteinase 8; NSD: non-surgical debridement; PDT: photodynamic therapy; T: treatment; TNF-α: tumor necrosis factor α.

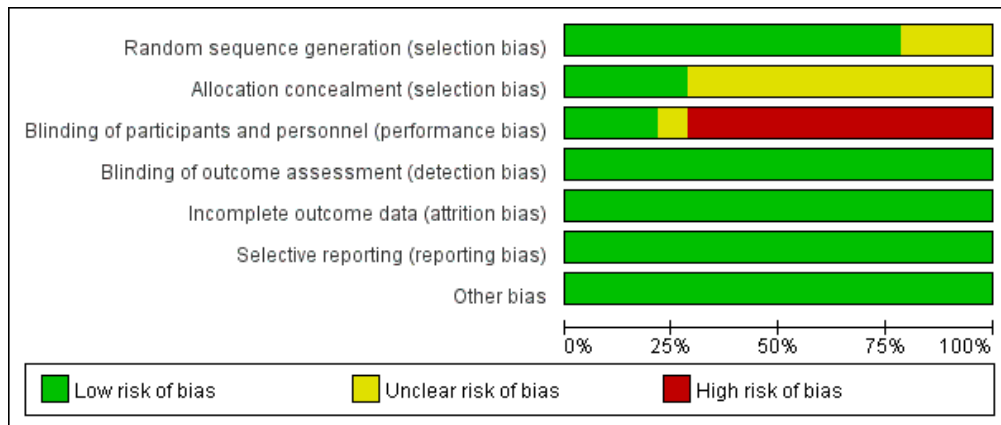


Figure 2. Risk-of-bias Assessment.

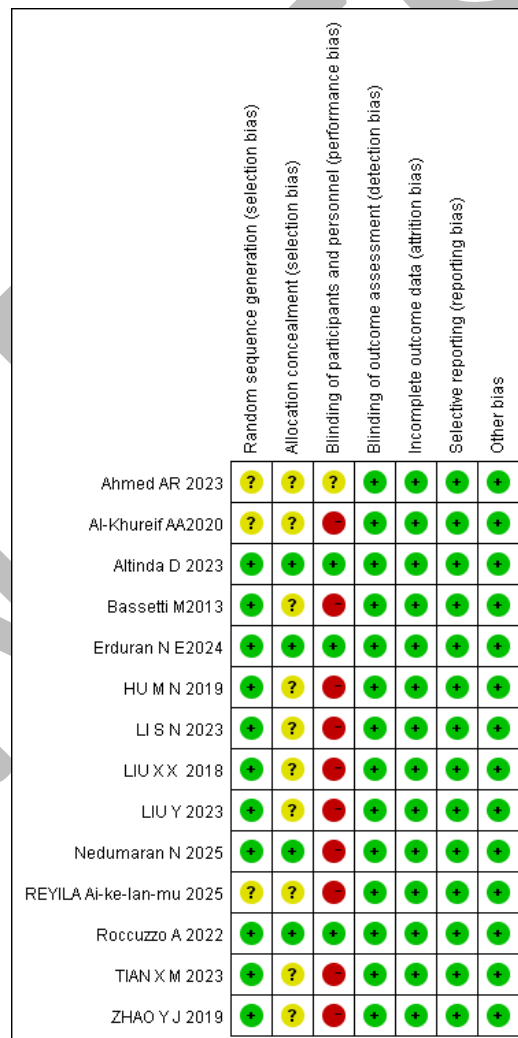


Figure 3. Summary of Risk of Bias.

Non-surgical Therapy Effects on Inflammation in Peri-implantitis

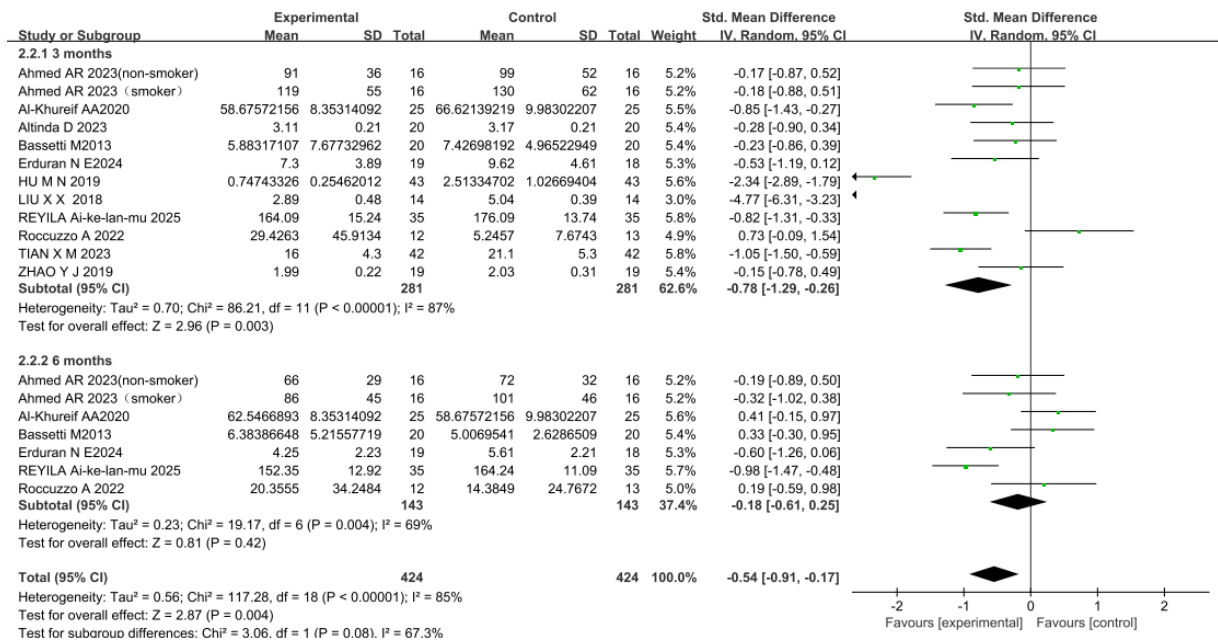


Figure 4. Meta-Analysis of IL-1 β .

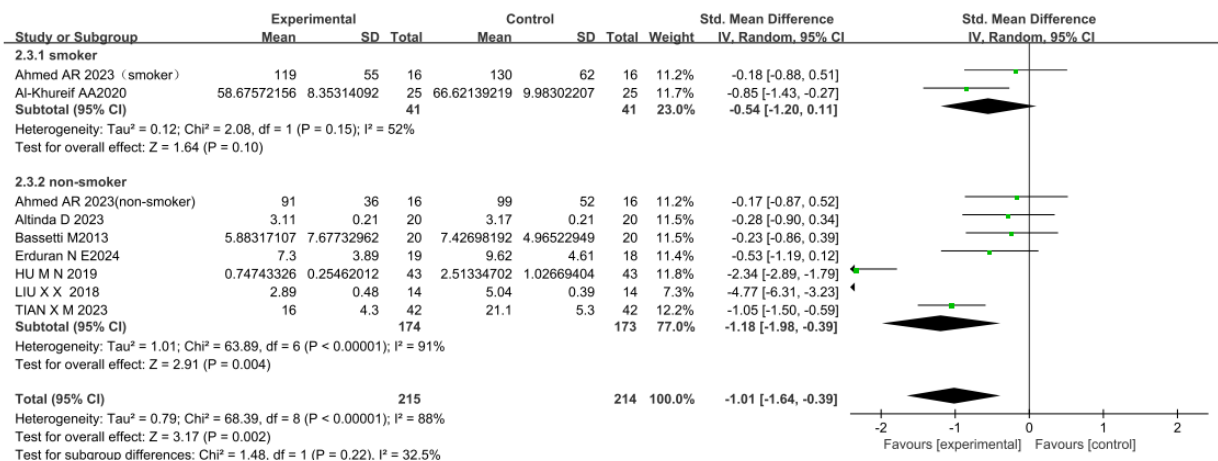
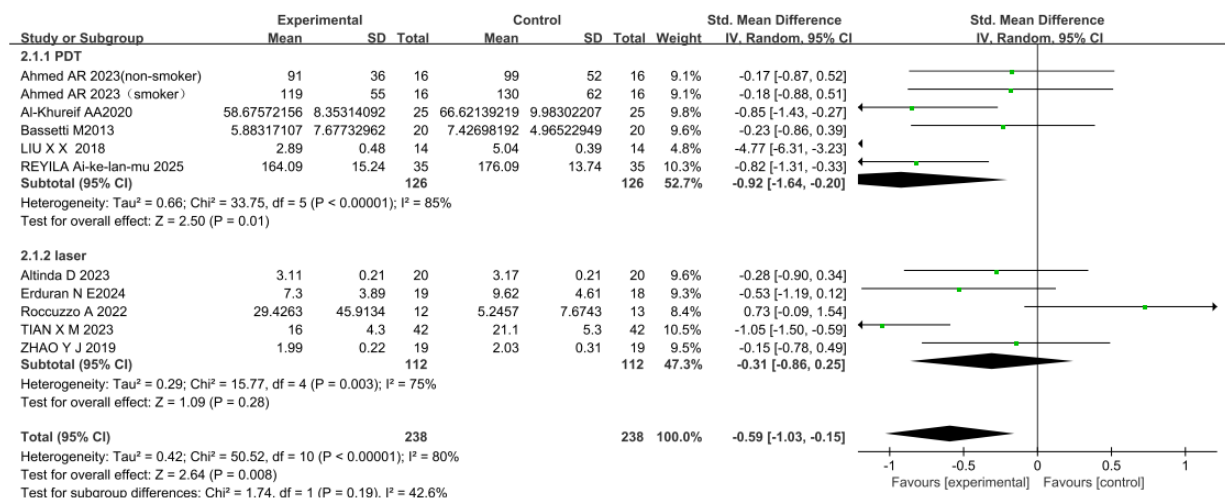
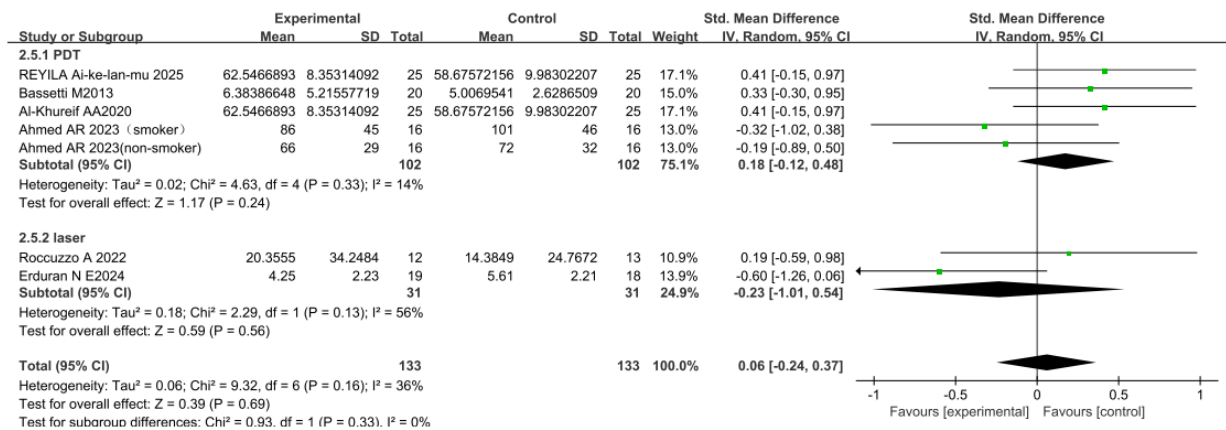


Figure 5. Subgroup Analysis of IL-1 β Levels at 3-Month Follow-up by Smoking Status.

Subgroup Analysis by Type of Non-surgical Treatment

Stratified analysis by type of non-surgical treatment showed substantial heterogeneity across studies ($I^2 > 50\%$; $p < 0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group receiving adjunctive PDT had a significantly greater reduction in IL-1 β levels than the control group (SMD, -0.92 ; 95% CI, -1.64 to -0.20 ; $p = 0.01$), whereas

the laser-based observation group did not differ significantly from the control group (SMD, -0.31 ; 95% CI, -0.86 to 0.25 ; $p = 0.28$), as shown in Figure 6. At the 6-month follow-up, neither the PDT group (SMD, 0.18 ; 95% CI, -0.12 to 0.48 ; $p = .24$) nor the laser group (SMD, -0.23 ; 95% CI, -1.01 to 0.54 ; $p = 0.56$) had a greater reduction in IL-1 β levels than the control group, as shown in Figure 7.

Figure 6. Subgroup Analysis of IL-1 β at 3-Month Follow-up by Type of Non-Surgical Adjuvant Therapy.Figure 7. Subgroup Analysis of IL-1 β at 6-Month Follow-up by Type of Non-Surgical Adjuvant Therapy.

IL-6

Four studies reported IL-6 data for patients with PI. Substantial heterogeneity was observed across studies ($I^2=78\%$; $p<0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group had a significantly greater reduction in IL-6 levels than the control group (SMD, -1.49; 95% CI, -2.07 to -0.91; $p<0.001$). Detailed data are shown in Figure 8.

TNF- α

Six studies reported TNF- α data for patients with PI. Substantial heterogeneity was observed across studies ($I^2=96\%$; $p<0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group had a significantly greater reduction in TNF- α levels than the control group (SMD, -1.84; 95% CI,

-3.05 to -0.63; $p=0.003$). Detailed data are shown in Figure 9.

Subgroup Analysis by Type of Non-surgical Treatment

Stratified analysis by type of non-surgical treatment showed substantial heterogeneity across studies ($I^2>50\%$; $p<0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group receiving adjunctive PDT had a significantly greater reduction in TNF- α levels than the control group (SMD, -0.80; 95% CI, -1.31 to -0.29; $p=0.002$), whereas the laser-based observation group did not have a greater reduction in TNF- α (SMD, -4.25; 95% CI, -12.57 to 4.07; $p=0.32$), as shown in Figure 10.

Non-surgical Therapy Effects on Inflammation in Peri-implantitis

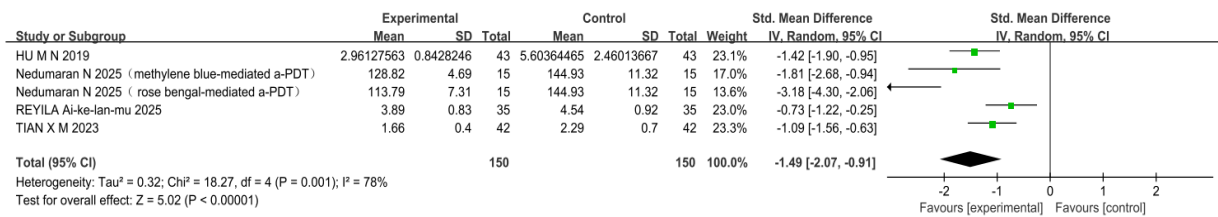


Figure 8. Meta-Analysis of IL-6.

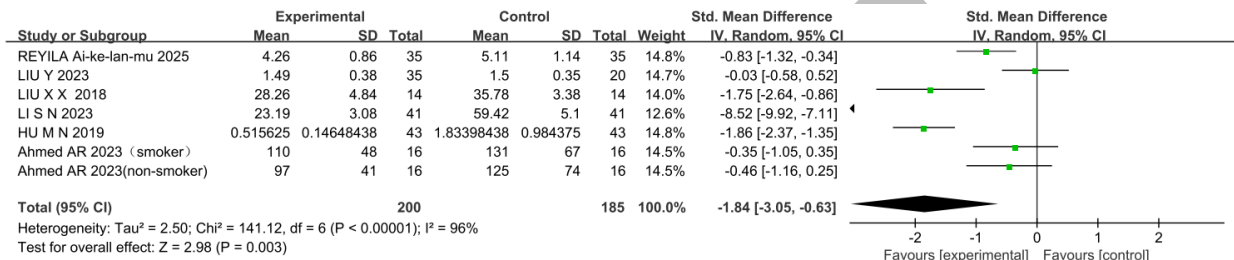


Figure 9. Meta-Analysis of TNF- α .

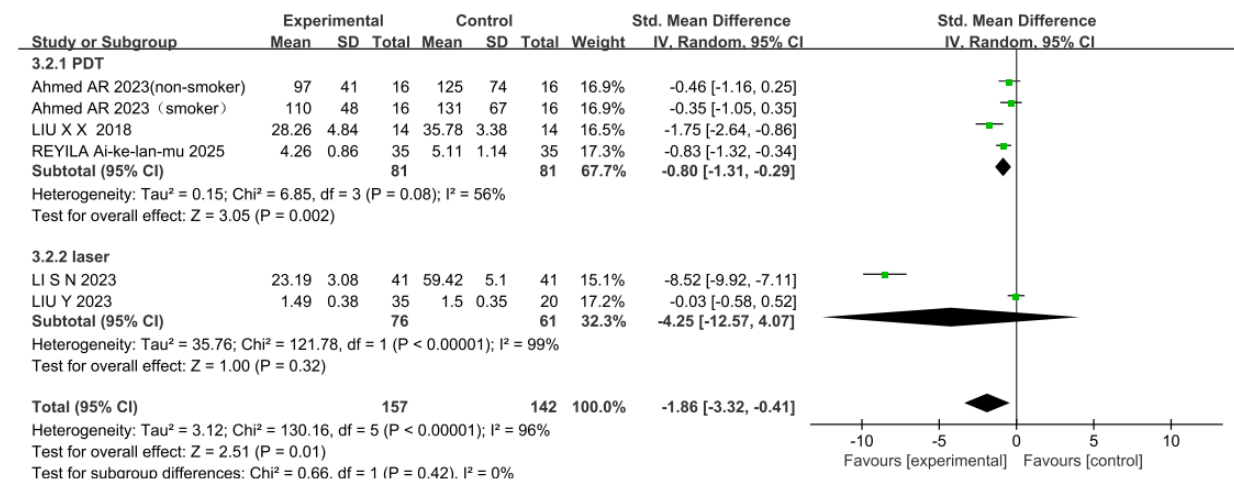


Figure 10. Subgroup Analysis of TNF- α at 3-Month Follow-up by Type of Non-Surgical Adjuvant Therapy.

MMP-8

Five studies reported MMP-8 data for patients with PI. Substantial heterogeneity was observed across studies ($I^2=96\%$; $p<0.001$); therefore, a random-effects model was used. At the 3-month follow-up, the observation group did not have a significantly greater reduction in MMP-8 levels than the control group (SMD, 0.08; 95% CI, -1.33 to 1.50; $p=0.91$). Detailed data are shown in Figure 11.

Sensitivity Analysis

For outcomes with high between-study heterogeneity ($I^2>50\%$), leave-one-out sensitivity

analyses were performed (Figures 12–16). The direction and statistical significance of the pooled effect sizes for IL-1 β at 3 and 6 months, IL-6 at 3 months, and TNF- α at 3 months remained unchanged, indicating that the conclusions for these outcomes were robust. However, for MMP-8 at 3 months, the direction of the pooled effect size reversed after exclusion of the studies by Bassetti et al⁶ and Liu et al¹⁶, indicating poor stability. Therefore, the findings for MMP-8 should be interpreted with caution.

Publication Bias

Egger linear regression tests were performed for each

outcome measure. A funnel plot was also constructed for the outcome reported by at least 10 studies, IL-1 β at 3 months. The p values for IL-1 β (3 months, $p=0.824$; 6 months, $p=0.394$), IL-6 (3 months, $p=0.072$), TNF- α (3 months, $p=0.105$), and MMP-8 (3 months, $p=0.125$) all exceeded .05, indicating no significant publication bias. The funnel plot for IL-1 β at 3 months showed some asymmetry, visually suggesting possible mild publication bias (Figure 17). This discrepancy with Egger test results

may be attributable to the limited number of studies ($n=11$), which reduced statistical power to detect true asymmetry; clinical heterogeneity, such as differences in intervention types, which may cause asymmetry unrelated to publication bias; and large effect sizes in some small studies, which may affect funnel plot symmetry. Therefore, although no significant publication bias was detected, the findings should be interpreted cautiously because of the visual asymmetry.

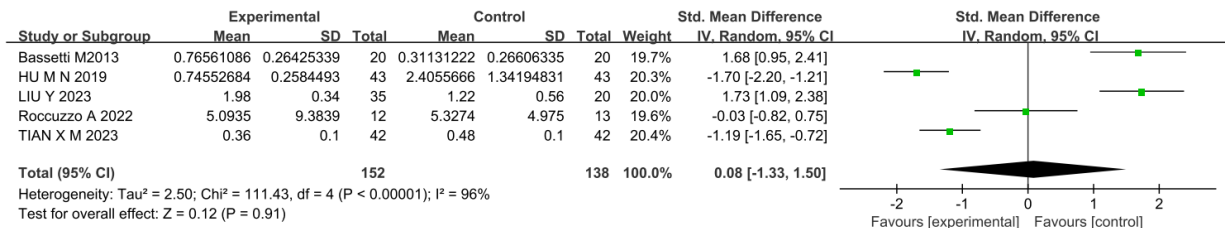


Figure 11. Meta-Analysis of MMP-8.

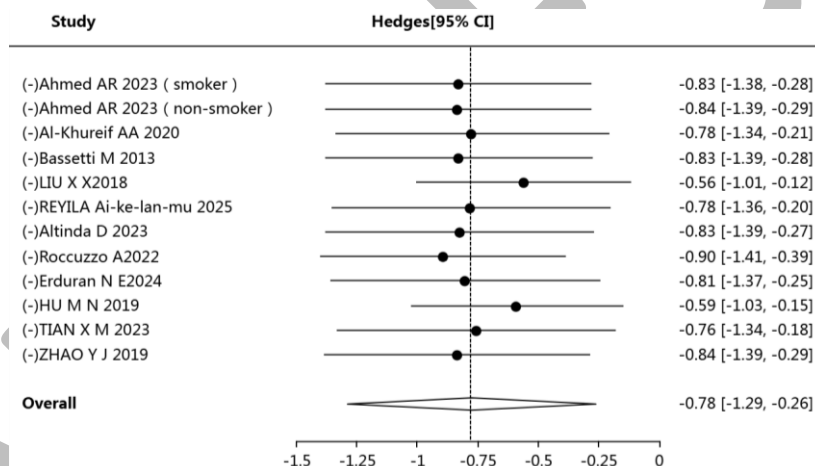


Figure 12. Sensitivity Analysis of IL-1 β at 3-Month Follow-up.

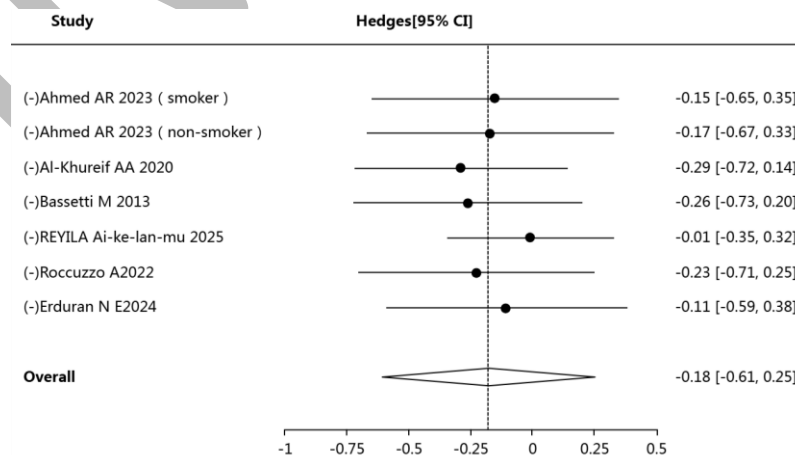
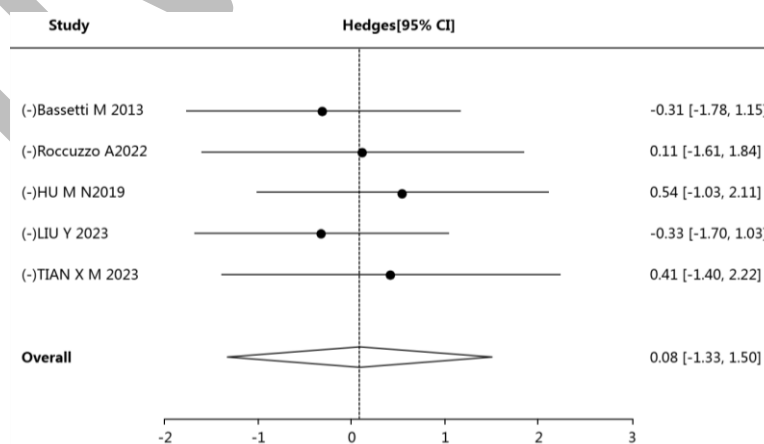
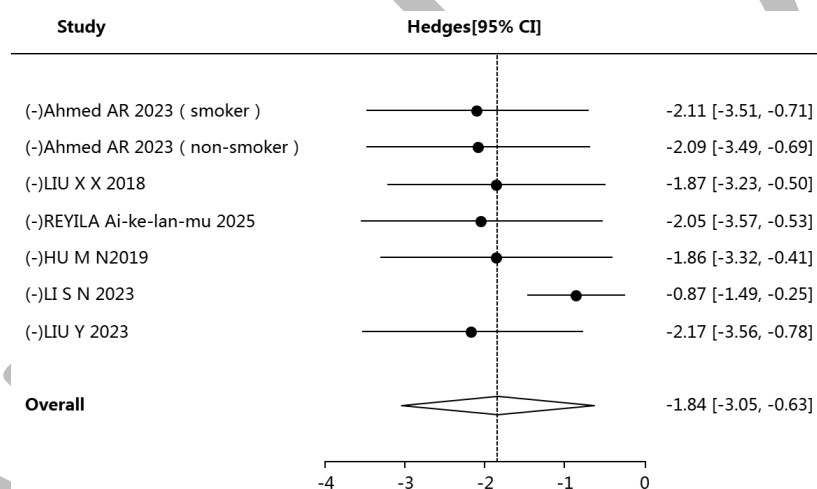
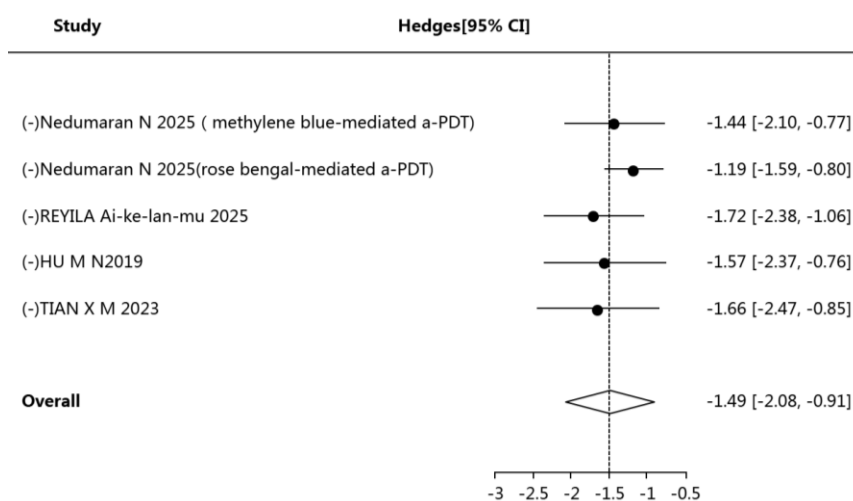


Figure 13. Sensitivity Analysis of IL-1 β at 6-Month Follow-up.

Non-surgical Therapy Effects on Inflammation in Peri-implantitis



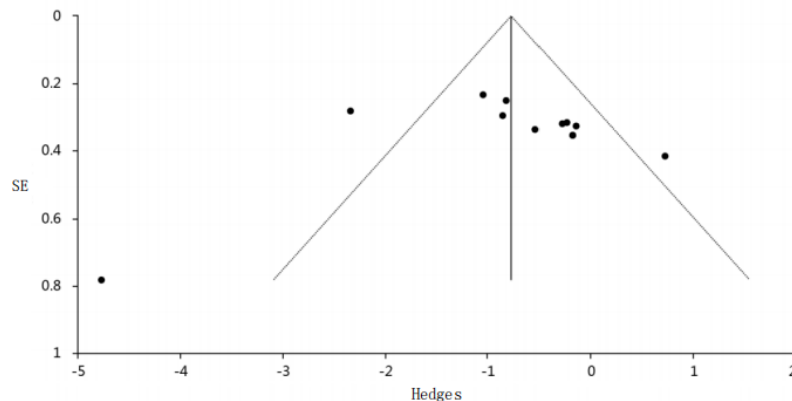


Figure 17. Funnel Plot.

Quality of Evidence

The GRADE system was used to rate the quality of evidence for each outcome. Ratings considered risk of bias, heterogeneity, publication bias, and sensitivity analyses.

IL-1 β , IL-6, and TNF- α : The overall quality of evidence was moderate and was downgraded 1 level because of substantial heterogeneity. Although most trials lacked operator blinding and had a high risk of performance bias, the inflammatory biomarkers were measured objectively in gingival crevicular fluid, minimizing reliance on blinding; therefore, no further downgrade was applied. The narrow 95% CIs and consistent direction of pooled effects indicated low imprecision and indirectness, with no additional downgrade. Given the insufficient number of included studies for some outcomes, funnel plot analysis was not conducted. Nevertheless, sensitivity analyses and the distribution of studies revealed no obvious publication bias.

MMP-8 at 3 months: The quality of evidence was low and was downgraded 1 level for heterogeneity and 1 level for result instability. Despite the high risk of performance bias across included studies, the outcome was an objective laboratory indicator, and no additional downgrade was applied. The pooled analysis showed significant heterogeneity ($I^2 > 50\%$), and subgroup analyses did not clarify its sources. Sensitivity analyses showed that excluding individual studies markedly altered the direction and magnitude of the pooled effect, indicating poor robustness. Because few studies were included, formal publication bias assessment was

unavailable; however, no obvious bias was observed, and no additional downgrade was assigned.

DISCUSSION

Although microbial infection initiates the pathogenesis of PI, immune-inflammatory responses mediated by inflammatory cytokines play a critical role in disease progression, and the balance of inflammatory cytokines determines disease severity.²¹ IL-1 β , IL-6, and TNF- α not only initiate and amplify inflammatory reactions but also promote osteoclastogenesis by activating collagenases and the receptor activator of nuclear factor κ B ligand pathway. MMP-8, produced by neutrophils, fibroblasts, and osteoclasts, contributes to collagen degradation in connective tissue and alveolar bone and is an important mediator of aggressive tissue destruction.^{22,23} Therefore, IL-1 β , IL-6, TNF- α , and MMP-8 are closely associated with the occurrence and progression of PI. Given the uncertain long-term efficacy, high cost, and increased risk of complications associated with surgical treatment, non-surgical therapies are commonly used in clinical practice to alleviate inflammation and improve prognosis.²⁴

At the 3-month follow-up, the observation group had significantly greater reductions than the control group in gingival crevicular fluid levels of IL-1 β , IL-6, and TNF- α . However, no statistically significant between-group difference in IL-1 β reduction was observed at the 6-month follow-up. These findings suggest that non-surgical treatment decreases inflammatory cytokine levels and relieves local inflammation in patients with PI at approximately 3 months, but the long-term anti-inflammatory effect may not be sustained. This may be

attributable to the inability of non-surgical treatment to completely eliminate residual pathogenic bacteria in deep peri-implant pockets and complex anatomical structures. At the 6-month follow-up, multiple factors, including oral microbial dysbiosis, local microtrauma, and dysregulation of the host innate immune response, may act synergistically to reactivate inflammatory pathways, leading to a rebound in proinflammatory cytokine levels in gingival crevicular fluid.

Exploratory subgroup analysis by treatment type showed that PDT significantly reduced IL-1 β and TNF- α levels at the 3-month follow-up, whereas laser-assisted therapy did not have statistically significant anti-inflammatory effects. A possible mechanism is that PDT uses a photosensitizer and a specific-wavelength light source, either a laser or light-emitting diode, under aerobic conditions. Upon photoexcitation, photosensitizer molecules transition from the ground state to the excited triplet state, generating reactive oxygen species and free radicals that kill gram-negative anaerobic bacteria, disrupt bacterial biofilms, regulate inflammatory pathways, and inhibit proinflammatory cytokine release, thereby producing local anti-infective and anti-inflammatory effects.²⁵ In contrast, although erbium-doped yttrium aluminum garnet (Er:YAG) lasers have antibacterial activity, their limited penetration into complex anatomical regions, such as peri-implant pockets and infrabony defects, prevents complete irradiation and reduces local decontamination efficiency. Incomplete removal of bacterial biofilms allows residual pathogens to sustain chronic inflammation, directly compromising therapeutic outcomes. Moreover, excessive irradiation duration or inappropriately high energy settings may induce local tissue hyperthermia, causing soft-tissue damage and thermal injury to surrounding bone and further attenuating anti-inflammatory efficacy.²⁶ Substantial heterogeneity in laser type, wavelength, output power, irradiation duration, and other parameters among included studies also weakened the overall therapeutic advantage of laser treatment. Previous studies found that Er:YAG laser did not effectively reduce anaerobic colony counts and had no significant regulatory effect on the oral pathogenic microbiota during long-term use.²⁷ In contrast, antimicrobial photodynamic therapy effectively reduced the total count of multiple PI-related pathogenic strains.²⁸ Related reviews similarly indicated that the microbiological benefits of Er:YAG and diode

lasers were weak and transient compared with PDT and did not produce durable inflammatory control.²⁹

Combined non-surgical treatment did not significantly improve MMP-8 levels at the 3-month follow-up, and sensitivity analysis showed poor stability, suggesting that this finding should be interpreted cautiously. The result may be related to the small number of included studies for this outcome and the substantial heterogeneity of interventions, including laser therapy, PDT, and probiotics. Future large-sample, multicenter RCTs with standardized intervention protocols and long-term follow-up are needed to verify the effects of these adjuvant therapies on MMP-8 and improve the reliability and clinical applicability of the findings.

Subgroup analysis by smoking status suggested a greater reduction in IL-1 β among non-smoking patients than among smoking patients. Given the limited number of studies in each subgroup, this finding remains exploratory and does not establish smoking as a modifier of treatment response. Smoking has been reported to adversely affect local blood supply and cellular immune responses in peri-implant tissues.²¹ These effects offer a possible biological explanation for the observed pattern, although the mechanisms underlying the subgroup findings were not directly assessed in this meta-analysis.

This study has several limitations. First, the small number of included studies reduced statistical power. Differences in intervention protocols and control measures increased heterogeneity and affected pooled effect estimates. Second, only short-term follow-up data from 3 to 6 months were available, and long-term efficacy data were lacking. Third, only published Chinese- and English-language literature was included, which may have introduced language bias and omitted unpublished negative findings. Fourth, substantial heterogeneity was present across most outcomes; too few studies were available for meta-regression, and subgroup analyses did not resolve the heterogeneity, reducing the stability and generalizability of the results. Fifth, small sample sizes in stratified analyses limited statistical power, and these exploratory findings should be interpreted cautiously. Sixth, sensitivity analysis showed instability for some outcomes. In addition, inconsistent methods for detecting inflammatory cytokines may have introduced measurement bias, and conversion of medians and interquartile ranges to means and standard deviations introduced inevitable estimation error.

Non-surgical treatment significantly reduced IL-1 β , IL-6, and TNF- α levels in the gingival crevicular fluid

of patients with peri-implantitis at the 3-month follow-up, demonstrating an anti-inflammatory effect. Exploratory subgroup analyses by smoking status and intervention modality suggested that inflammatory improvement was greater in non-smoking patients than in smoking patients and that PDT had a more favorable efficacy trend than laser therapy. However, these benefits were not sustained at the 6-month follow-up.

STATEMENT OF ETHICS

This systematic review and meta-analysis was based exclusively on data from previously published studies and did not involve the direct recruitment of human participants, the collection of identifiable personal information, or animal experimentation. Therefore, approval by an institutional ethics committee and additional informed consent were not required.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

All data generated or analyzed during this systematic review and meta-analysis are included in this article and the cited publications. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Chen L, Tong Z, Luo H. Titanium particles in peri-implantitis: distribution, pathogenesis, and prospects. *Int J Oral Sci.* 2023;15(1):49.
2. Cui Z, Wang P, Gao W. Microbial dysbiosis in periodontitis and peri-implantitis: pathogenesis, immune responses, and therapeutic. *Front Cell Infect Mi.* 2025;15:1517154.
3. Berglundh T, Mombelli A, Schwarz F. Etiology, pathogenesis, and treatment of peri-implantitis: a European perspective. *Periodontol 2000.* 2024;10–1111.
4. Smeets R, Henningsen A, Jung O, Heiland M, Hammächer C, Stein JM. Definition, etiology, prevention, and treatment of peri-implantitis: a review. *Head Face Med.* 2014;10:34.
5. Bassetti M, Schär D, Wicki B, et al; Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: 12-month outcomes of a randomized controlled clinical trial. *Clin Oral Implan Res.* 2014;25(3):279–87.
6. Fornel DG, Ferrisse TM, de Oliveira AB, Fontana CR. Photodynamic therapy can modulate the nasopharyngeal carcinoma microenvironment infected with the Epstein-Barr virus: a systematic review and meta-analysis. *Biomedicine.* 2023;11(5):1344.
7. Ahmed AR, Kamran MA, Suleman G, Sharif RA, Alamreay AAM, Sulaiman SA. Novel use of chloro-aluminum phthalocyanine-assisted photodynamic therapy helps in periimplant healing among smoking patients. *Photodiagn Photodyn Ther.* 2023;41:103193.
8. Al-Khureif AA, Mohamed BA, Siddiqui AZ. Clinical, host-derived immune biomarker, and microbiological outcomes with adjunctive photochemotherapy compared with local antimicrobial therapy in the treatment of peri-implantitis in cigarette smokers. *Photodiagn Photodyn Ther.* 2020;30:101684.
9. Altindal D, Alkan EA, Calisir M. Evaluation of the effectiveness of diode laser therapy in conjunction with nonsurgical treatment of peri-implantitis. *J Periodontal Implan.* 2023;53(5):376–87.
10. Erduran NE, Guncu GN, Akman AC, et al; Evaluation of the effect of adjunctive diode laser application on peri-implant crevicular fluid biomarker levels: a randomized controlled trial. *Clin Oral Invest.* 2024;28(8):459.
11. Nedumaran N, Rajasekar A. Impact of rose bengal-mediated antimicrobial photodynamic therapy adjunctive to mechanical debridement on clinical, microbiological, and immunological parameters in peri-implantitis: a parallel, single-blinded, randomized controlled trial. *Laser Med Sci.* 2025;40(1):300.

Non-surgical Therapy Effects on Inflammation in Peri-implantitis

12. Chambrone L, Wang HL, Romanos GE. Non-surgical mechanical therapy of peri-implantitis with or without repeated adjunctive diode laser application: a 6-month double-blinded randomized clinical trial. *Clin Oral Implan Res.* 2022;33(9):900–12.
13. Reyila Ai-ke-lan-mu, Reanguli A-bu-du-wei-li, Guo T, et al; Application effect and microbial ecological reconstruction analysis of probiotic regulation combined with photodynamic therapy in peri-implantitis. *J North Sichuan Med Coll.* 2025;40(8):991–6.
14. Hu MN, Sun F, Zhou YH. Clinical and microbiological effects of *Lactobacillus reuteri* as adjuvant therapy for peri-implantitis. *Chin J Microecol.* 2019;31(8):934–9.
15. Li SN, Song W. Effect of semiconductor laser on treatment of mild-to-moderate periimplantitis. *Chin J Nosocomiol.* 2023;33(13):2032–6.
16. Liu Y, Fan ZH, Yang CHSH. Short-term effect of implant grinding and polishing combined with drugs and laser therapy on peri-implantitis. *J Mod Stomatol.* 2023;37(6):401–6.
17. Liu XX, Ma X, Yang SY. Efficacy of photodynamic therapy as an adjunct in the treatment of peri-implantitis. *Acta Univ Med Anhui.* 2018;53(4):645–8.
18. Tian XM, Liu YQ, Li L, et al; Clinical study on joint application of Er,Cr:YSGG laser and implant polishing in treating peri-implantitis. *Chin J Laser Med Surg.* 2023;32(6):306–12.
19. Zhao YJ, Li RH, Ren G, et al; Effect of low-level laser treatment combined with initial periodontal therapy on IL-8, b-FGF, and IL-1 β content in gingival crevicular fluid in peri-implantitis. *Int J Biomed Eng.* 2019;42(2):130–3.
20. Soysal F, Unsal B, Isler SC, Akca G, Bakirarar B, Ozcan M. Evaluation of salivary stress markers and inflammatory cytokine levels in patients with peri-implantitis. *Clin Oral Invest.* 2024;28(5):290.
21. Chmielewski M, Piloni A. Current molecular, cellular, and genetic aspects of peri-implantitis disease: a narrative review. *Dent J-Basel.* 2023;11(5):134.
22. Guarnieri R, Reda R, Di Nardo D, et al; Expression of IL-1 β , IL-6, TNF- α , and a-MMP-8 in sites with healthy conditions and with periodontal and peri-implant diseases: a case-control study. *J Dent Res Dent Clin Dent Prospects.* 2024;18(2):135–42.
23. Nart J, Pons R, Valles C, Esmatges A, Sanz-Martín I, Monje A. Non-surgical therapeutic outcomes of peri-implantitis: 12-month results. *Clin Oral Invest.* 2020;24(2):675–82.
24. Elsadek MF. Effectiveness of 2 photosensitizer-mediated photodynamic therapies for treating moderate peri-implant infections in patients with type 2 diabetes mellitus: a randomized clinical trial. *Photodiagn Photodyn Ther.* 2023;43:103643.
25. Almoharib H. Erbium-doped yttrium aluminum garnet (Er:YAG) lasers in the treatment of peri-implantitis. *Cureus J Med Science.* 2025;17(1):e78279.
26. Chen JH, Lin YC, Kung JC, et al; Efficacy of Er:YAG laser for peri-implantitis treatment and microbiological changes: a randomized controlled trial. *Laser Med Sci.* 2022;37(9):3517–25.
27. Świder K, Dominiak M, Grzech-Leśniak K, Matys J. Effect of different laser wavelengths on periodontopathogens in peri-implantitis: a review of in vivo studies. *Microorganisms.* 2019;7(7):189.
28. Neophytou C, Vlachodimou E, Kaklamanos EG, Sakellari D, Papadimitriou K. Microbiological effects of laser-assisted non-surgical treatment of peri-implantitis: a systematic review and meta-analysis of randomized controlled trials. *Dent J-Basel.* 2026;14(1):49.
29. Sun D, Li Z, Li D, Wu B, Ma Y. Laser combined with mechanical debridement enhances pain relief and inflammation control in the management of periodontitis with peri-implantitis. *Am J Transl Res.* 2025;17(7):5698–5709.