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SYSTEMATIC REVIEWS AND META-ANALYSIS

Use of IL-1 β, IL-6, TNF-α, and MMP-8 biomarkers to distinguish peri-implant diseases: A systematic review and meta-analysis

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Abstract

Objective: To investigate the use of peri-implant crevicular fluid (PICF) interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and matrix metalloproteinase-8 (MMP-8) biomarkers in distinguishing between healthy implants (H), peri-implant mucositis (MU), and peri-implantitis (PI).

Material and Methods: Electronic using three databases (Pubmed, EMBASE, and Cochrane) and manual searches were conducted for articles published up to March 2018 by two independent calibrated reviewers. Meta-analyses using a random-effects model were conducted for each of the cytokines; IL-1β, IL-6, and TNF-α, to analyze standardized mean difference (SMD) between H and MU, MU and PI, H and PI with their associated 95% confidence intervals (CI). Qualitative assessment of MMP-8 was provided consequent to the lack of studies that provide valid data for a meta-analysis.

Results: Nineteen articles were included in this review. IL-1β, IL-6, and TNF-α, levels were significantly higher in MU than H groups (SMD: 1.94; 95% CI: 0.87, 3.35; $P < .001$, SMD: 1.17; 95% CI: 0.16, 3.19; $P = .031$ and SMD: 3.91; 95% CI: 1.13, 6.70; $P = .006$, respectively). Similar results were obtained with PI compared to H sites (SMD: 2.21, 95% CI: 1.32, 3.11; $P < .001$, SMD: 1.72; 95% CI: 0.56, 2.87; $P = .004$ and SMD: 3.78; 95% CI: 1.67, 5.89; $P < .001$, respectively). IL-6 was statistically higher in PI than MU sites (SMD = 1.46; 95% CI: 0.36, 2.55; $P = .009$); while IL-1ß increase was not significant. Despite absence of meta-analysis, MMP-8 show to be a promising biomarker in detection of PI in literature.

Conclusion: Within the limitations of this study, pro-inflammatory cytokines in PICF, such as IL-1ß and IL-6, can be used as adjunct tools to clinical parameters to differentiate H from MU and PI.

KEYWORDS
cytokines inflammation, dental implants, meta-analysis, systematic review

1 | INTRODCUTION

"Peri-implant diseases" collectively describe plaque—associated pathological conditions that develop inflammatory lesions in tissues around implants.[1] A continuum exists between health and peri-implant diseases, categorized into peri-implant mucositis (MU) and peri-implantitis (PI). MU is the precursor to PI, with around 43%-48% prevalence rate among implants.[2–4] PI is distinguished by progressive loss of supporting bone beyond initial biological bone remodeling; when compared to MU,[5] and has a prevalence rate of 12%-43%.[1,6]

Clinical and radiographic evaluations are the most used methods in diagnosing MU and PI. Although easily applicable, clinical parameters alone do not assess the risk rate, onset, activity, and progression of peri-implant destructive changes.[7–10] Biomarkers are host response molecules that have been investigated in determining disease and its severity in conjunction with clinical assessment.[11,12] Pro-inflammatory

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cytokines are some of the most investigated biomarkers in peri-implant diseases, as they play an important role in cascading inflammatory responses that are cellular and vascular.[13] The presence of polymorphonuclear cells (PMN) and abundance of fibroblast matrix metalloproteinase-8 (MMP-8) had also been shown to be pertinent to the early detection of PI, which usually follows the release of those cytokines.[14,15] The destruction of connective tissue is a significant determinant of the progression of peri-implant lesions that is essentially driven by MMP-8. This collagenase is known to be the major MMP detected in periodontitis and is thought to be a potential biomarker of PI.

IL-1β, TNF-α, IL-6, and MMP-8 have been investigated in conjunction with bleeding on probing, gingival index, and probing depths, to prevent and profoundly comprehend pathogenesis of peri-implant diseases.[16] Their concentrations also vary markedly in normal biologic, pathogenic conditions as well as after therapeutic interventions.[17] Peri-implant crevicular fluid (PICF), similar to gingival crevicular fluid around teeth, can be an indicator of inflammatory exudates, through which those biomarkers could be collected. PICF is easily accessible, non-invasive, and sequentially determinable; therefore, if variation in cytokine and MMP-8 levels matches severity and classification of diseases in reference to health, routine biomarkers testing could become a personalized diagnostic tool in clinical practice.[11,18]

A published systematic review and meta-analysis, including articles up to 2013, investigated TNF-α and IL-1β in PICF, showing robust levels in disease compared to health, but no significant difference between MU and PI.[19] Nonetheless, the extent of inflammation markedly increases from MU to PI, as shown by the majority of clinical studies. Additionally, IL-6 is one of the most investigated pro-inflammatory cytokines between healthy and diseased peri-implant tissues.[20–25] MMP-8 was very useful to monitor the rapid destruction of connective tissue that marks the progression of MU and PI.[18,26]

Hence, this study aimed at (1) investigating the potential use of IL-1β, IL-6, TNF-α, and MMP-8, as biomarkers of implants health, peri-implant mucositis, and peri-implantitis conditions in PICF; (2) attempting to develop a recognizable pattern of cytokines and MMP-8 release; and (3) identifying factors that may influence results of previous studies to minimize discrepancies in future investigations.

2 | MATERIAL AND METHODS

This systematic review and meta-analysis was performed and written following the 27-item PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al 2009). The PRISMA checklist is attached to the appendix of this article (Supporting Information Checklist 1).

2.1 | Focus question

The focus question was developed considering the Population, Intervention, Comparison, and Outcome (PICO) elements (Stone 2002) and as follows: Could cytokine and MMP-8 levels in the PICF be used to distinguish between health (H), MU, and PI?

P: Systemically healthy subjects who received dental implants.

I: IL-1β, IL-6, TNF-α, and MMP-8 biomarkers can be used to differentiate between H, MU, and PI.

C: Investigating the presence or absence of a difference in the cytokine and MMP-8 levels between implants with H, MU, and PI.

O: There is a difference in the level of IL-1β, IL-6, TNF-α, and MMP-8 between (1) H versus MU; (2) H versus PI; and (3) MU versus PI.

2.2 | Search strategy

Electronic and manual literature searches were conducted by two reviewers (IG, ZC) independently, using PubMed/MEDLINE, EMBASE, and Cochrane Library up to March 2018 without language restriction. For the PubMed library, the search terms were as follows: (dental implant[MeSH Terms]) OR dental implantation[MeSH Terms]) OR implant[Title/Abstract]) OR peri-implant crevicular fluid[Title/Abstract]) OR PICF[Title/Abstract]) OR peri-implant sulcus fluid[Title/Abstract]) OR PSF[Title/Abstract]) AND (cytokines[MeSH Terms]) OR biomarkers[MeSH Terms]) OR interlukin[Title/Abstract]) OR IL[Title/Abstract]) OR tumor necrosis factor[Title/Abstract]) OR TNF[Title/Abstract] OR MMP-8[Title/Abstract]). For the EMBASE, the search strategy was: ("tooth implantation"/de OR "tooth implant"/exp OR "dental implant":ti,ab,kw) AND ("biological marker"/de OR "cytokine"/exp OR "biomarker":ti,ab,kw OR "interlukin":ti,ab,kw OR "tumor necrosis factor":ti,ab,kw). For the Cochrane Library, (cytokine OR biomarker) AND implant was applied in Title, Abstract, and Keywords in Trials.

Additionally, to complete the survey, a manual search of periodontics/implantology-related journals from March 1995 to March 2018, including *Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, *Journal of Periodontology*, *Clinical Implant Dentistry and Related Research*, *European Journal of Oral Implantology*, *International Journal of Oral and Maxillofacial Implants*, *Implant Dentistry*, *Journal of Oral Implantology*, *International Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery and International Journal of Periodontics and Restorative Dentistry*. The related reviews[9,19,27] and references of selected studies were further scanned for potentially relevant articles.

According to the selection criteria, titles and abstracts of the search results were screened, and then the full-text articles screen was conducted. The level of agreement between the reviewers (IG, ZC) for potentially relevant articles was calculated using k statistics. A consent on final decision was reached by discussion with the senior author (HLW).

2.3 | Data extraction and selection criteria

Data from the eligible studies were extracted by two reviewers (IG, JZ) independently. The inter-reviewer disagreement was resolved by discussion as well as consultation with senior author (HLW). Corresponding authors were contacted in cases of missing or unclear data.

For this systematic review, eligible studies met the following inclusion criteria: (1) original cross-sectional and longitudinal prospective clinical studies with the collection of pro-inflammatory cytokines in PICF from individuals with PI or MU; (2) studies analyzed protein

expression by enzyme-linked immunosorbent assay (ELISA) or flow cytometry using a cytometric bead array system. The exclusion criteria comprised of: (1) animal, in vitro studies, case reports, and reviews; (2) studies with quantification of pro-inflammatory cytokines in tissue biopsies or saliva; (3) only analysis of osteogenic markers; (4) unreported exact numbers of cytokine levels; (5) fluid collection during early osseointegration; (6) unclear peri-implant disease criteria; and (7) unreported anti-inflammatory and antibiotic medication in inclusion criteria.

2.4 | Risk of bias assessment

The criteria used to assess the quality of selected studies is the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. This constituted of 14 questions and provided guidelines for evaluating the research question, study population, exposure, outcomes, follow-up rate, and statistical analyses. Consequently, studies are rated good and fair. This was completed by two examiners (IG, ZC) independently. The possibility of publication bias (see Appendix Figure A1) was assessed with Egger linear plots for continuous-data elements. A significant publication bias is found if $P < .05$.[28]

2.5 | Statistical analysis

Stata 14.0 (StataCorp LP, College Station, Texas) was used to conduct all of the statistical analyses. The standardized mean difference (SMD) between two groups was analyzed with random effects model to compare the IL-1β, IL-6, and TNF-α levels between H and MU, H and PI, as well as MU and PI. SMD was used rather than the weighted mean difference (WMD) since the measurement units for each biomarker varied between studies; that is, in accordance with Cochrane guidelines.[29] Heterogeneity was estimated by the Q statistic (significant at $P < .1$) and quantified with the I^2 test. The value of $I^2 \geq 75\%$ suggests high or "considerable/substantial" heterogeneity. Moderate heterogeneity is deduced from results showing 30%-60% and 0%-40% may not be important.[30] Galbraith plots analyses were conducted to investigate the potential source of heterogeneity among studies.[31]

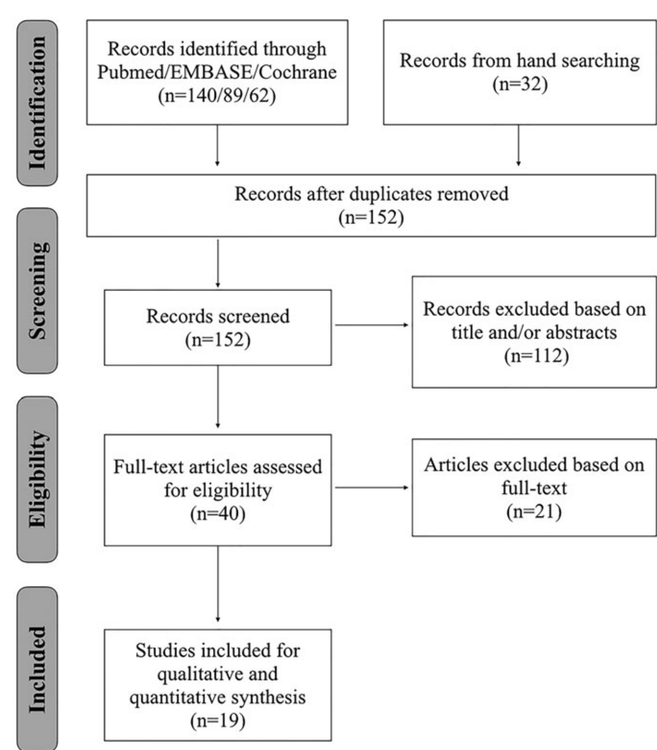

FIGURE 1 PRISMA flow diagram of the. Study selection process

3 | RESULTS

3.1 | Study selection

The literature selection process is illustrated by a PRISMA flowchart (Figure 1). Initial screening yielded a total of 291 records, 140 articles

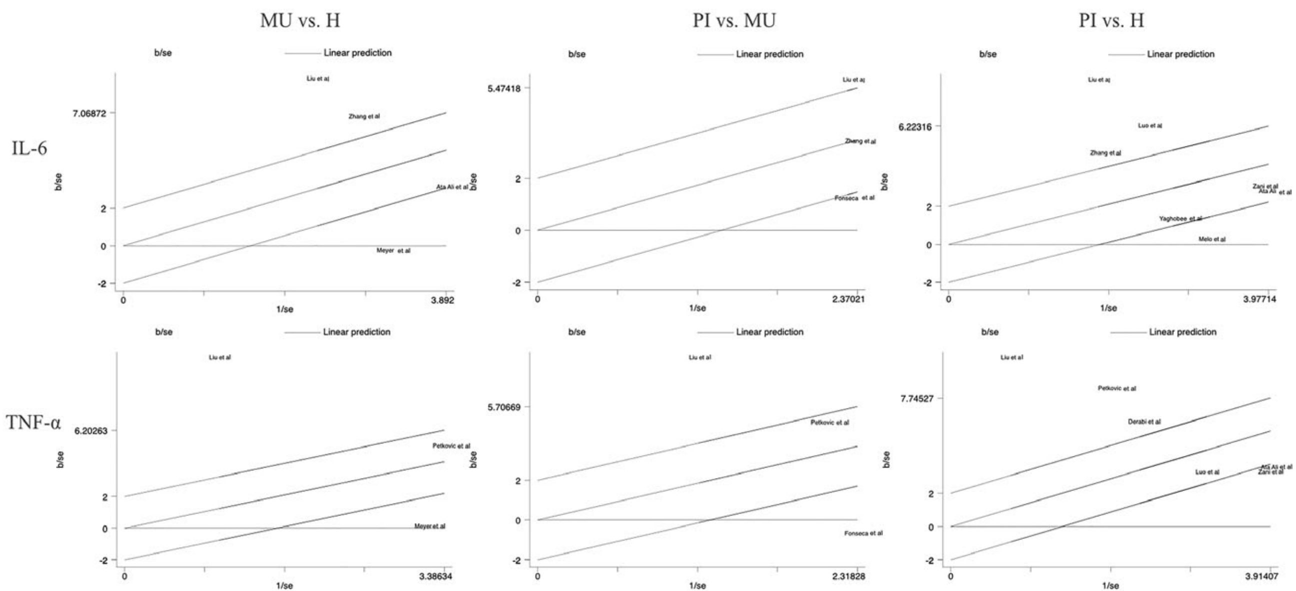

FIGURE A1 Galbraith plot assessing heterogeneity of studies included in the comparison of IL-6 (and TNF-α) between H and MU, MU and PI, H and PI

TABLE 1 Summary of excluded articles

Author	Biomarkers	Reasons
Ataoglu et al	IL-1β, TNF-α, neutrophil elastase specific peptide	Lack of a healthy control and diseased test groups
Che et al	IL-1β, OPN	IL-1β was not compared between healthy control and diseased test groups
Hultin et al	IL-1β, lactoferrin, elastase	Lack of valid data (mean, SD)
Kajale et al	IL-1β	Diseased and healthy conditions were not defined at the two time-points of measurement
Lachmann et al	IL-1β, PAI-2, PGE-2	Patients' inclusion criteria did not include control of additional anti-inflammatory factors
Ramseier et al	IL-1β, MMP-8, PISF, GCF, MMP-1/TIMP-1, MMP-3	Lack of clear disease conditions
Renvert et al	IL-1β, IL-6, IL-8, IL-10, IL-17, IL-1ra, TNF-α, MIP-1α, PDGF, VEGF	Only provide peri-implantitis group
Severino et al	IL-6,8,10,17	Lack of valid data (mean, SD)
Severino et al	IL-6, IL-10, IL-17, IL-33	Lack of valid data (mean, SD)
Murata et al	IL-1 β, osteocalcin	Concentrations of IL-1β in health was not provided
Xie et al	IL-1 β, IL-6, IL-8, TNF-α, and HMG1	Healthy implants were defined as those which received peri-implant surgery. Cytokine data identical to those in Luo
Luo et al	IL-1β, IL-6, IL-8, TNF-α, HMGB1, HMGN2	Healthy implants were defined as those which received peri-implant surgery. Cytokines data identical to those in Xie et al
Güncü et al	IL-1β, IL-10, RANKL, OPG	Unclear distinguishing criteria of nature of peri-implant disease
Melo et al	IL-1β, IL-6	Unclear distinguishing criteria of the nature of peri-implant disease
Thierbach et al	MMP-8	Therapeutic intervention at baseline; that is, prior to acquiring biomarker samples
Wohlfort et al	OPG, MMP-8 and IL-6	Therapeutic intervention at baseline; that is, prior to acquiring biomarker samples
Gao et al	MMP-8, MMP-13, IL-17, and IL-1β	Healthy implants were not defined
Basegmez et al	PGE-2, MMP-8	Insufficient definition of peri-implant disease. MMP-8 was investigated longitudinally in the course of wound healing after implant placement
Borsani et al	MMP-1, MMP-3, MMP-8, MMP-13, TIMP-1, COL I, III, IV, and V	Gingival biopsies rather PICF were the source of biomarkers
Kivelä-Rajamäki et al	Laminin-5 2-chain, MMP-8	Single time point sampling
Nomura et al	TIMP-1, MMP-1, MMP-8	MMP-8 was investigated longitudinally in the course of wound healing after implant placement. MMP-8 in PICF of PI was not compared to H PICF

Abbreviations: COL, collagen, plasminogen activator inhibitor-2; HMGB1, high mobility group nucleosomal binding domain 2; ILs, interleukins; OPG, osteoprotegrin; RANKL, receptor activator of nuclear factor kappa-B ligand; TIMP, tissue inhibitor of metalloproteinases.

via PubMed, 89 via EMBASE, and 62 via Cochrane Library. Additionally, 32 records were found by hand-searching. After duplicates discarded, 152 records remained. The review of the titles and abstracts resulted in 42 articles selected for full-text screening, 21 of them were then excluded with reasons listed in Table 1. Finally, 19 eligible articles (26; 32; 33; 34; 35; 36; 37; 15; 38; 25; 24; 39; 23; 22; 40; 11; 2; 41; 42) were included in this systematic review and quantitative synthesis. The details of the included studies are reported in Table 2. The *k* value for inter-reviewer agreement of potentially relevant articles was 0.84 (title/abstract screening) and 0.89 (full-text screening), indicating a consistent agreement between the two reviewers. A consent on final decision was reached by discussion with another reviewer (HLW).

3.2 | Description of the studies

The most studied cytokine was IL-1β (*n* = 14), followed by IL-6 (*n* = 8) and TNF-α (*n* = 6). Other cytokines, IL-4, IL-8, IL-10, IL-12, and IL-17, were also linked to peri-implant diseases. MMP-8 was investigated in 12 studies, of which eight were excluded.

All included studies were either cross-sectional or longitudinal experimental ones. Regarding the age of patients, the most common range was between 30 and 60 years. Meyer in 2017, showed the highest age group of patients, with a mean age of 77. Among the 19 included studies, five used ELISA R&D System; a type of sandwich immunoassay where two highly specific antibodies are used to detect a target analyte.[22,23,25,35,39] Eight used other ELISA kits,[2,11,15,26,32,36,38,42] two CBA assays,[33,34] three multiplexes,[25,37,40] and one Luminex kit.[41]

3.3 | Meta-analyses of IL-1β, IL-6, and TNF-α

For IL-1β, there were five articles[22–25,35] comparing its level between H and MU (Figure 2A). In one article,[23] there were two subgroup of MU (ie, early and advanced MU), so we included both arms in meta-analysis. MU group showed significantly higher IL-1β level than H group (SMD: 1.94; 95% CI: 0.87, 3.35; $P < .001$). The heterogeneity between studies was significant ($I^2 = 92.1\%$, $P < .001$). The Galbraith plot (Figure 2B) showed that the considerable heterogeneity was generated by one study.[25] With this study removed, the heterogeneity

TABLE 2 Characteristics of all included articles

Study (author, year)	Study design	Implant function time	Patients and implants numbers (H/MU/PI)	Mean age (years)	Characterization of peri-implant tissues	Clinical parameters (H/M/PI)
Ata Ali et al (2013)	Cross sectional	N/A	H: Pts: 22 (9M/13F); I: 54 MU: Pts: 12 (5M/7F); I: 23	H: 63.6 (10.4) MU: 60.2 (7.4)	**H:** PD < 4 mm, absence of clinical signs of inflammation of the peri-implant mucosa, and no radiographic bone loss **MU:** Gingival redness, swelling, BoP, and without radiographic signs of bone loss	**mPI** H: 0.96 (1.03); MU: 1.70 (1.22) **mGI** H: 0.63 (0.92); MU: 1.39 (0.78) **PD (mm)** H: 2.72 (0.59); MU: 3.55 (0.40)
Meyer et al (2017)	Short cohort	N/A	H: 20 (10M/10F) MU: 20 (10M/10F)	H: 77.0 (5.7) Mu: 77.0 (5.7)	**H:** Ti implants in good general and oral health; without any periodontal diseases **MU:** Participants refrained from oral hygiene practices while being monitored in weekly intervals for 3 weeks	**PI** H: 0.00 [0.00;0.00]; MU: 2.00 [1.56;2.44] **BOP (%)** H: 0.00 [0.00;0.10]; MU: 0.71 [0.58;0.85] **PD (mm)** H: 2.83 [2.73;3.08]; MU: 3.13 [2.88;3.33]
Salvi et al (2012)	Cross sectional	N/A	H: 15 (8M/8F); I: 15 MU: 15 (8M/8F); I: 15	58.7 (10.9)	**H:** Healthy or treated periodontal conditions **MU:** The subjects were asked to refrain from oral hygiene practices for a period of 21 days	**PI** H: 0.00; MU: 1.33 **mGI** H: 00; MU: 1.50 **PD (mm)** H: 3.00; MU: 2.83
Teixeira et al (2016)	Cross sectional	≥6 months	MU: 10 (4M/6F); I:10 PI: 14 (5M/9F);I:14	61.7 (7.1)	**MU:** Patients with clinically inflamed sites and no significant radiographic bone loss (barely reaching the first thread) **PI:** Patients with inflamed sites and bone loss involving two or more implant threads	**CAL** MU: 1.4 (0.7); PI: 1.5 (0.7) **BOP (%)** MU: 66.7 (26.1); PI: 82.1 (24.9) **PD (mm)** MU: 3.3 (0.8); PI: 3.9 (0.9)
Zhang et al (2005)	Cross sectional	≥3 months	H: 23 MU: 34 PI: 8 (25F/31M)	31.2	**H:** No pockets deeper than 4 mm, had no plaque or gingival inflammation and no bone loss (BL) **MU:** Pockets deeper than 4 mm in at least one site, GI ≥ 1, PLI ≥ 1, no radiographic evidence of bone loss (BL) **PI:** PD > 4 mm in at least one site, GI ≥ 1, PLI ≥ 1, bone loss (BL) >20% in at least one site	**PI** H:0; MU: 1.5 (1-3); PI: 2.0 (2-4) **GI** H:0; MU: 1.5 (1-3); PI: 2.5 (1-4) **PD (mm)** H: 1.93 (0.96); MU: 5.05 (0.72) PI: 7.04 (1.52)
Yaghobee et al (2014)	Cross sectional	≥1 year	H:8 PI:8 (4F/4M)	N/A	**H:** No BoP, no PD > 3 mm, gingiva was pink and had stippling, and there was no sign of exposure of implant threads in the parallel radiograph	N/A

(*Continues*)

TABLE 2 (Continued)

Study (author, year)	Study design	Implant function time	Patients and implants numbers (H/MU/PI)	Mean age (years)	Characterization of peri-implant tissues	Clinical parameters (H/M/PI)
					PI: BoP, presence of a pocket (PD > 5 mm), and exposure of at least two implant threads in a parallel radiograph	
Panagakos et al (1996)	Cross sectional	≥6 months	H Pts: 13; I: 17 Early PI:27 Advanced PI: 6	55	**H:** Minimal or no gingival inflammation, evidenced by lack of localized erythema or BOP, no pockets greater than 4 mm, CAL < 2 mm, and no BL **Early PI:** Presence of gingival inflammation, BpP, no pockets greater than 6 mm, no loss of attachment greater than 2 mm, BL ≤ 30% **Advanced PI:** Interproximal probing depths greater than 6 mm and with approximately the same amount of CAL. BL > 30% and BOP	**PI** 0 (40 pt), 1 (9 pt) Pi: 1 (4 pt), 2 (7/11 pt) **GI** H: 0; PI: 2 **PD (mm)** H: ≤3; PI: >4
Kao et al (1995)	Preliminary study	≥37 months	H: Pts:12 (5M/7F); I: 12 PI: Pts:12 (5M/7F); I: 12	33-64	**H:** Those who exhibited no radiographic evidence of bone loss, no pocket depth greater than 4 mm, and no pain **PI:** Rapidly increasing pocket depth (≥2 mm increase over 6 months), suppuration, radiographic evidence of bone loss, pain, and loss of resonation with tapping	N/A
Aboyoussef et al (1998)	Clinical control	≥6 months	H: 37 PI: 37	N/A	**H:** No gingival inflammation, lack of localized erythema or bleeding on probing; pockets ≤4 mm; attachment loss ≤2 mm; and no evidence of radiographic bone loss **Early PI:** Gingival inflammation; bleeding on probing; pockets ≤6 mm; loss of attachment ≤2 mm; evidence of bone loss not exceeding 30%; and no mobility	N/A
Liu et al (2017)	Cross sectional	65.2 (4.7) months	H: 22 (6M/16F); I: 39 MU: 42 (27M/15F); I: 24 PI: 16 (7M/9F); I: 16	43 (11.7)	**H:** Dental implant sites with no sign of inflammation (PD <3, sGI ≤ 1) **MU:** Sites exhibiting signs of inflammation (PD ≥ 3, sGI > 1) without a radiographic sign of bone loss **PI:** Sites with PD ≥ 3, GI > 1 and a radiographic sign of bone loss	**mPI** H: 1.17 (0.04); MU: 1.76 (0.63); PI: 2.11 (0.41) **GI** H: 0.47 (0.09); MU: 2.11 (0.33); PI: 2.47 (0.51) **mBI** H: 0.11 (0.27); MU: 2.11 (0.41); PI :2.29 (0.43) **PD (mm)** H: 1.94 (0.42); MU: 3.66 (0.93); PI: 5.54 (1.13)
Ata Ali et al (2015)	Cross sectional	≥24 months	H: Pts: 22 (9M/13F); I: 54 PI:	H: 63.3 (10.4) PI:	**H:** Probing pocket depth (PPD) <4 mm absence of clinical signs of inflammation of the peri-implant mucosa, and without	**mPI** H: 0.96 (1.03); PI: 1.25 (1.15)

(*Continues*)

TABLE 2 (Continued)

Study (author, year)	Study design	Implant function time	Patients and implants numbers (H/MU/PI)	Mean age (years)	Characterization of peri-implant tissues	Clinical parameters (H/M/PI)
			Pts:13 (6M/7F); I:24	52 (7.7)	radiographic bone loss **PI:** Implant with a probing depth ≥4 mm and signs of acute Pi (loss of supporting bone as estimated on radiographs, bleeding on probing or suppuration) and no implant mobility	**mGI** H: 0.63 (0.92); PI: 2.71 (0.46) **PD (mm)** H: 2.72 (0.59); PI 5.15 (0.68)
Fonseca et al (2012)	Case control	≥6 months	MU: 12 PI: 10 (6M/16F)	MU 65 (9.4) PI 59.4 (11.8)	**MU:** Patients who showed inflamed sites with bone loss around the implants no deeper than the first implant's thread and pocket depth ≤3 mm **PI:** Patients who showed inflamed sites with at least one implant with bone loss around two or more threads of the implant and pocket depth ≥4 mm	**PD (mm)** MU: 2.2 (0.5); PI: 5.1 (0.8)
Petkovic et al (2010)	Case control	12-36 months	H: 49 Early MU: 41 Advanced MU: 11 (9F/81M)	55	**H:** Patients with clinically healthy gingival tissue around dental implants **Early MU:** Mild inflammation; no BoP and PD 3 or 4 mm **Advanced MU:** Patients with advanced stage MU (GI = 2)	**PI** H: 0 (40 pt), 1 (9 pt), 2 (0); early MU: 0 (3 pt), 1 (23 pt), 2 (4 pt); advanced MU: 0 (0 pt), 1 (4), 2 (7 pt) **GI** H: 0; early MU: 1; advanced MU: 2 **PD (mm)** H: ≤3, early MU: 3 < PD < 4; advanced MU: ≥4
Casado et al (2013)	Case control	6–8 months	H: 10 MU: 10; I: 60 PI: 10; I: 50 (12F/18M)	49.5-57.4	**H:** No clinical signs of inflammation in the peri-implant mucosa and no signs of bone loss in all regions **MU:** BoP, red mucosa and swelling, spontaneous bleeding, but no radiographic signs of pathologic bone loss **PI:** Showed clinical signs of inflammation, including implant mobility and suppuration in some cases, and radiographic signs of bone loss	**BoP (%)** H: 0.2; MU: 1.0; PI: 1.0 **PD (mm)** H: 1.1 (0.5); MU 2.9 (0.5); PI 4.2 (1.4)
Darabi et al (2013)	Case control	≥1 year	PI: 24 H: 18	28-57	**H:** No inflammation in peri-implant mucosa **PI:** Suppuration, erythema, PD > 6 mm, BoP and progressive bone loss	**PD (mm)** H: 3.7 (1.6); PI: 6.2 (1.1)
Zani et al (2016)	Cross sectional	≥1 year	H: 14 (16 site) PI: 32 (47 site) (41F/11M)	56 (8)	**H:** PD < 5 mm, no BOP or SUP and no radiographic bone loss >2 mm **PI:** Presence of at least one site with PD > 4 mm with BoP and/or suppuration and radiographic evidence of bone loss ≥2 mm	**PD (mm)** H: 3.3 (1.2); PI: 5.6 (0.8) **BoP (%)** H: 14%; PI: 99%

(*Continues*)

TABLE 2 (Continued)

Study (author, year)	Study design	Implant function time	Patients and implants numbers (H/MU/PI)	Mean age (years)	Characterization of peri-implant tissues	Clinical parameters (H/M/PI)
Wang et al (2016)	Case control	≥6 months	H: 34 (14F/20M) PI: 34 (19F/15M)	H: 62.1 (10.4) PI: 65.3 (10.3)	**H:** Absence of radiographic implant threads exposure **PI:** BoP and/or suppuration in combination with PD ≥ 5 mm and radiographic bone loss with the exposure of the implant surface below the first thread based on periapical radiograph	**BoP (%)** H: 11 (5.4); PI 147 (72.0) **PD (mm)** H: 3.2 (0.3); PI: 5.8 (0.4)
Janksa et al (2016)	Pilot study	3 months-14 years	27 implants *N* = 54 F and S	43-75	**H:** MMP-8 levels <8 ng/mL **MU:** MMP-8 levels 8-20 ng/mL **PI:** MMP-8 levels >20 ng/mL; PD ≥ 5 mm	N/A
Arakwa et al (2012)	Longitudinal study	4.73 years	H: 60; I: 153 Severe PI: 4; I:9 (33F/31M)	68.50 (6.7)	**H:** AVBL <0.3 mm. **Mild PI:** AVBL between 0.3 and 0.6 mm. **Severe PI:** AVBL >0.6 mm	N/A

Study (author, year)	Assessed biomarkers	Type of assay/kit	Biomarkers mean value/(SD)	Main results
Ata Ali et al (2013)	IL-1β IL-6	Human inflammation cytometric bead array (CBA) system (BD Biosciences) and FACS analysis (BD Biosciences)	**IL-6: (pg/mL)** H: 0.53(0.64); MU 0.09 (0.49) **IL-1β: (pg/mL)** H: 21.2; MU: 42.5	IL-6: MU > H. Although IL-1β was increased in the MU group, there was no statistically significant difference versus the H implant group. The percentage of PPD, mPI and mGI scores, were significantly higher around MU compared to H. (*P* > .05)
Meyer et al (2017)	IL-1β, IL-1 (IL-1ra), IL-6, IL-8, IL-17, basic-FGF, G-CSF, GM-CSF, IFN-c, MIP-1b, TNF-α, VEGF	Multiplex fluorescent bead-based immunoassay	**IL-1β (pg/mL)** H: 80.9 (38146); MU: 166.8 (116.6294.4) **IL-6 (pg/mL)** H: 1.9 (1,5.6); MU: 1.6 (0.3,2.4) **TNF-α (pg/mL)** H: 7.1 (5.7,17.8); MU: 8.7 (2.3,12.3)	IL-1β increased significantly with plaque accumulation
Salvi et al (2012)	MMP-8 IL-1β	ELISA (R&D Systems Europe Ltd, Abingdon, UK)	**IL-1β (pg/site)** H: 3.06(1.02 4.1); MU: 7.91 (2.13, 11.9) **MMP-8 (pg/site)** H: 438.11 (32.14-1468.26); MU: 1678.26 (795-2460.66)	The CF levels of MMP-8 were statistically significantly higher at implants compared with teeth. The CF IL-1β levels did not differ statistically significantly between teeth and implants
Teixeira et al (2016)	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN-c, sCD40L, and TNF-α	Bead-based multiplex immunoassay. (Bio-PlexProTM Human TH17Cytokine Panel – Bio-Rad)	**IL-1β (pg/mL)** Mu: 155.0 [78.1; 269.1]; PI: 230.9 [96.3; 370.4] **IL-6 (pg/mL)** Mu: 6.3 [5.2; 10.3]; PI: 8.2 [4.7; 45.8]	There was no SSD in cytokine levels in MU sites among the three groups. In group 2, PD was lower in MU than PI (*P* < .001)

(*Continues*)

TABLE 2 (Continued)

Study (author, year)	Assessed biomarkers	Type of assay/kit	Biomarkers mean value/(SD)	Main results
Zhang et al (2005)	IL-6	ELISA (Bio-Source, Camarillo, California)	**IL-6 (ng/mL)** H: 1.74(1.66); MU: 5.53 (1.57); PI: 9.36(5.56)	IL-6 level in the PICF was significantly associated with PI, GI, PD
Yaghobee et al (2014)	IL-1β IL-6	ELISA test (Biocompare, South San Francisco, California) software program (R&D Systems, Minneapolis, Minnesota)	**IL-1β (pg/mL)** H: 13.55 (8.59); PI: 20.76 (6.86) **IL-6 (pg/mL)** H: 6.43(5.03); PI: 8.87 (5.84)	IL-1β with PI were significantly higher than around H implants. A SSD was found in the level of IL-6 between those with PI and H implants
Panagakos et al (1996)	IL-1ß TNF-α IL-8 MIP-1	ELISA (R&D, SAD) Quantokine Immunoasay for human IL-1 β (cat. number DLB50), Human TNF-alpha (cat. Number DTA50), Human IL-8 (cat. number D800C), human MIP-1 alpha	**IL-1β (pg/site)** H: 56.47(15.55se); early PI: 460.77 (35.67se); advanced PI: 191.10 (21.60se)	IL-1ß may be modulating attachment loss in implants suffering from PI. Thus, IL-1ß may be used to monitor disease progression
Kao et al (1995)	IL-1β	ELISA (CistronBiotechnology, Pine Brook, New Jersey)	**IL-1β (pg/μL)** H: 120.4 (73.4); PI: 385.95 (209)	IL-1ß was approximately three times that at healthy sites
Aboyoussef et al (1998)	IL-1β PGE_2 MMPs	ELISA (Cistron, Pine Brook, New Jersey); EIA (Advanced Magnetics, Cambridge, Massachusetts); substrate polyacrylamide zymography Substrate polyacrylamide zymography of MMP bands	**IL-1β (pg/site)** H: 13.0 (5.2); early PI: 609.5 (54.3)	PGE_2 and MMP levels are not reliable as markers for distinguishing between H and diseased implants IL-1ß increased by "sixfold" in early PI versus H implants. Meanwhile, no SSD was found in the PGE2 levels around H and PI implants
Liu et al (2017)	HMGB1, IL-1β, IL-6, IL-8, and TNF-α	High-sensitivity multiplex map human cytokine immunoassay (R&D)	**IL-1β (pg/mL)** H: 227.7 (18.5); MU: 483.3 (65.9); PI: 872.2 (114.3) **IL-6 (pg/mL)** H: 144.3 (33.1); MuU: 288.7 (45.9); Pi: 537.2 (151.4) **TNF-α (pg/mL)** H: 178.3 (11.9); MU: 289.4 (7.4); Pi: 402.6 (24.5)	There was a high correlation between the HMGB1 level and the expression of IL-1β and TNF-α and a moderate correlation between the HMGB1 level and the expression of IL-6 and IL-8. An increasing tendency of sGI, mPI, mBI, and PD accompanied by the progress of inflammation
Ata Ali et al (2015)	IL-6, Il-1β, IL-10, TNF-α	Human inflammation cytometric bead array (CBA) system (Becton Dickinson, BD Biosciences, San Diego, California)	**IL-1β (pg/mL)** H: 21.2 (24.2); PI: 58.5 (84.8) **TNF-α (pg/mL)** H: 0.25 (0.56); PI: 1.08 (1.49)	Concentrations of IL-1β ($P < .01$), IL-6 ($P < .01$), IL-10 ($P < .05$), and TNF-α ($P < .01$) with PI compared to H peri-implant tissue. mGI and PD were statistically significant

(*Continues*)

TABLE 2 (Continued)

Study (author, year)	Assessed biomarkers	Type of assay/kit	Biomarkers mean value/(SD)	Main results
Fonseca et al (2012)	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IFN-γ, and TNF-α	Multiplex map human cytokine immunoassay (Millipore Corporation, Billerica, Massachusetts)	**IL-1β (pg/mL)** Mu: 0.14 (0.18); PI: 0.45 (0.48) **TNF-α (pg/mL)** Mu: 0.54 (1); PI: 0.29 (0.22)	Elevated levels of IL-1β in PICF were characteristic to Pi BoP difference was not significant between MU and PI. PD was lower in MU when compared to PI (*P* = .001)
Petkovic et al (2010)	MIP-1α, TNF-α, IL-1β, IL-8	ELISA (R&D, SAD) (Quantokine Immunoasay DLB50)	**TNF-α (pg/mL)** H: 0.8 (1.85); MU: 19.8 (23.6); PI: 130.4 (74.1) **IL-1 β (pg/mL)** H: 12.6 (14.8); MU: 178.7 (208.1); PI: 1705.3 (2410.6)	Positive correlation was noted in the control group between IL-1β and TNF-a and between MIP-1a and IL-8 in the group with early MU Control group had significantly lower concentrations of biomarkers compared to both groups with MU (*P* < .01 for IL-1β and *P* < .001 for TNF-a, MIP-1a, and IL-8)
Casado et al (2013)	IL-1 β IL-10	ELISA kits Duo Set ELISA Development System; R&D System, Inc, Minneapolis, Minnesota)	**IL-1β (pg/mL)** H: 67.51 (62.9); MU: 325.89 (235.17); PI: 439.89 (182.67)	Mean IL-1β levels lower in H and MU. No significant difference occurred between diseased groups (*P* < .05) IL-10 levels were higher in H patients others (*P* = .0001)
Darabi et al (2013)	IL-17 TNF-α	ELISA reader model awareness-Statfax2100	**TNF-α (pg/site)** H: 4.5 (8.9); PI: 38.9 (9.3)	TNF-α and IL-17 significantly increased (*P* = .000) and can be used as diagnostic markers
Zani et al (2016)	IL-17, IL-1-ra, Flt-3L, IL-10, sCD40L, GM-CSF, TNFα, PDGF-BB, IL-15	Luminex Millipore Corporation, Billerica, Massachusetts The human cytokine 20-plex (magnetic bead panel) Millipore kit	**IL-1 β pg/mL** H: 1.15 (0.91); PI: 1.75 (0.81) **IL-6 pg/mL** H: 0.57 (0.51); PI: 0.97 (0.54) **TNF-α pg/mL** H: 0.44 (0.35); PI: 0.74 (0.38)	There was SSD between the two clinical categories for IL-13, PDGF-BB, IL-15, sCD40L, IL-17, IL-1β, IL-2, IL-6, and TNF-α
Wang et al (2016)	IL-1β, MMP-8, TIMP-2, VEGF, OPG	Quantibody Array Raybiotech ELISA	**IL-1 β pg/mL** H: 44.60 (53.00); PI: 135.83 (97.30) **MMP-8 pg/mL** H: 6029.18 (2132.07); PI: 5943.13 (1183.24)	IL-1β, VEGF, and OPG increased significantly in PI compared to H. The ability to diagnose diseased sites was enhanced by *T. denticola* combined with IL-1 β, VEGF and TIMP-2.MMP-8 and OPG disease-diagnostic accuracy increases when combined with a microbial profile

(*Continues*)

TABLE 2 (Continued)

Study (author, year)	Assessed biomarkers	Type of assay/kit	Biomarkers mean value/(SD)	Main results
Janksa et al (2016)	MMP-8	DentoTest aMMP8 (dentognostics GmbH, Jena, Germany)	**MMP-8 pg/mL** <8 ng/mL: 88.9% (S); 74% (F) 8-20 ng/mL: 9.3% (S); 20.4% (F) >20 ng/mL: 1.8% (S); 5.6% (F)	A positive correlation between PICF volume and collagenase-2 (MMP-8) level from fundus and distal area, but not from mesial and superficial areas. Additionally, samples from fundus can be more useful in early detection of disease; when compared to PICF volume measurements alone
Arakwa et al (2012)	MMP-1 MMP-8 MMP-13	BCA protein assay reagent kit (PIERCE, Rockford, Illinois)	**MMP-8 mg/mL** H: 204.75 (37.83); PI: 357.11 (90.2)	MMP-8 was the only collagenase observed in PI sites; confirming that it may be a possible predictor for active periods of peri-implantitis bone loss

Abbreviations: AVBL, average bone loss; BoP, bleeding on probing; CD, cluster differentiation; F, fundus; GI, gingival index; GM-CSF, granulocyte - macrophage colony-stimulating factor; IFN, interferons; IL, interleukin; mGI, modified gingival index; MIP, macrophage inflammatory protein; MMPs, metalloproteinases; MU, mucositis; OPG, osteoprotegrin; PD, pocket depth; PDGF-BB, platelet derived growth factor beta polypeptide; PGE2, prostaglandin E2; PI, peri-implantitis; S, sulcular; TIMP, tissue Inhibitor of metalloproteinases; VEGF, vascular endothelial growth factor.

decreased effectively (I^2 = 9.4%, P = .353), and the result remained significant (SMD: 1.21, 95% CI: 0.89, 1.53; P < .001).

Four studies[25,35,37,40] compared IL-1β release level between implants with MU and PI (Figure 2C). The result demonstrated that the IL-1β in PI site was similar to that in MU site (SMD: 1.52, 95% CI: −0.03, 3.07; P = .055), with significant heterogeneity among these studies (I^2 = 91.5%, P < .001). The Galbraith plot (Figure 2D) also showed that the considerable heterogeneity was generated by one study.[25] The heterogeneity decreased effectively (I^2 = 0.0%, P = .734) upon removal of that study, and the result became significant (SMD: 0.60, 95% CI: 0.12, 1.08; P = .015).

Nine studies[2,11,25,32,34,35,38,39,41] reported the difference in IL-1β between H and PI (Figure 2E). Meta-analysis of these data showed IL-β release was much higher in PI compared to H sites (SMD: 2.21, 95% CI: 1.32, 3.11; P < .001). However, high degree of heterogeneity was noted (I^2 = 92.6%, P < .001). The Galbraith plot (Figure 2F) demonstrated that the heterogeneity came from three studies.[25,32,35] After excluding the data of these studies, the homogeneity test showed moderate heterogeneity among the remaining 12 studies (I^2 = 43.6%, P = .115), and results showed that the SMD was 1.06 (95% CI: 0.71-1.42; P < .001).

3.4 | Meta-analysis of IL-6 and TNF-α

When comparing H and MU, four studies[24,25,33,42] reported levels of IL-6 and three studies[23–25] reported the levels of TNF-α. Statistical differences were found in both cytokines (Figures 3A and 4A), which indicated that in MU sites, the release of IL-6 and TNF-α was increased (SMD: 1.17; 95% CI: 0.16, 3.19; P = .031 and SMD: 3.91; 95% CI: 1.13, 6.70; P = .006, respectively). Regarding MU versus PI, there were three studies on IL-6[25,37,42] (Figure 3B). PI group showed significantly higher levels of IL-6 than that in MU group (SMD = 1.46; 95% CI: 0.36, 2.55; P = .009). For PI versus H, IL-6 was investigated in five studies[2,25,34,41,42] (Figure 3C) and TNF-αwere reported in four studies[23,25,34,36,41] (Figure 4B). Results showed that PI group has higher releasing level in both IL-6 (SMD: 1.72; 95% CI: 0.56, 2.87; P = .004) and TNF-α (SMD: 3.78; 95% CI: 1.67, 5.89; P < .001). Meta-analyses revealed high heterogeneity between these studies, with I^2 ranged from 80.3% to 98.1%. The Galbraith plot (Appendix Figure A1) did not show any specific papers contributing to heterogeneity.

3.5 | MMP-8 results

Only five articles were included in this review investigating MMP-8 in healthy conditions versus peri-implant diseases.[11,15,22,26,32] In Salvi et al 2012, MMP-8 increased significantly between H and MU. The three other articles compared H to PI.[11,15,26] Mean values and SD of MMP-8 levels were only provided in two of the three articles[11,26]; thus, meta-analysis could not be performed. Nonetheless, MMP-8 was found in elevated amounts in PICF collected from a total of 85 implants; that were diagnosed with peri-implant diseases. Fifteen implants had MU and 70 had PI. Arakawa et al only found MMP-8 in PICF. The sensitivity of technique and depth of PICF samples were marked both high and significant.[15] Further, a combination of

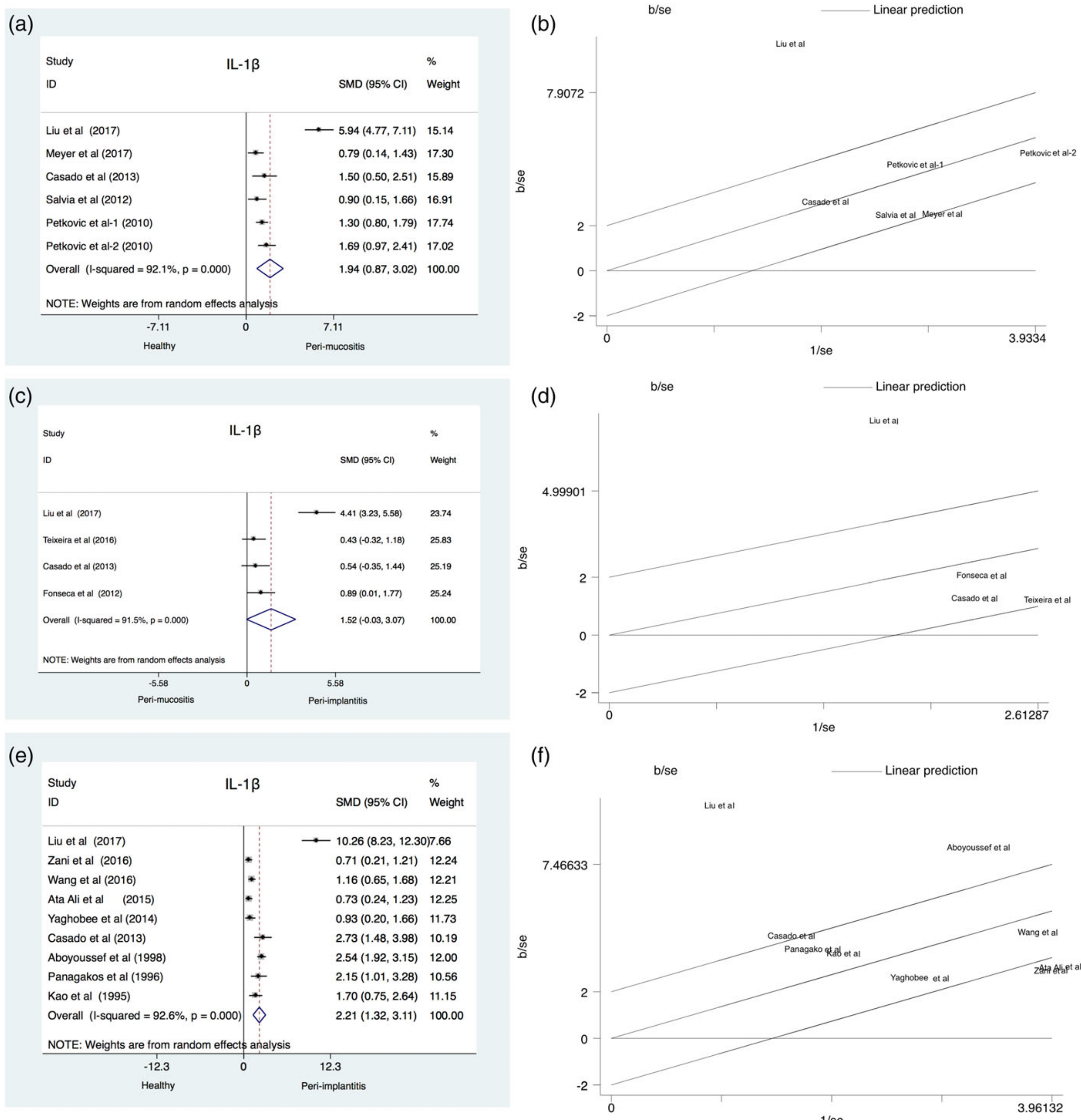

FIGURE 2 Forest plots presenting standard mean difference (SMD) of IL-1β comparing H with MU (A), MU with PI (C), and H with PI (E). Galbraith plot assessing heterogeneity of studies included in the comparison of IL-1β between H and MU (B), MU and PI (D), H and PI (F). ES = effect sizes; b/se = standardized estimates; 1/se = precision

microbiological profiling and MMP-8 found to have increased the accuracy of results previously obtained.[11]

3.6 | Quality and risk assessment

According to NIH Quality Assessment tool, risk assessment of bias was conducted. A study reporting less than 4 (No/NR) was defined with low risk. Any higher scores than 4 increased the bias risk and were concluded to be fair. Ten studies were regarded "good" and 9 were "fair." These were also shown in Table 3.

3.7 | Publication bias

The publication bias was presented by Egger test in Appendix Figure A2. For IL-1β, there was no evidence of publication bias, according to Egger's test, in the comparison of H to MU sites (P = .159), MU and PI (P = .08). However, publication bias was found

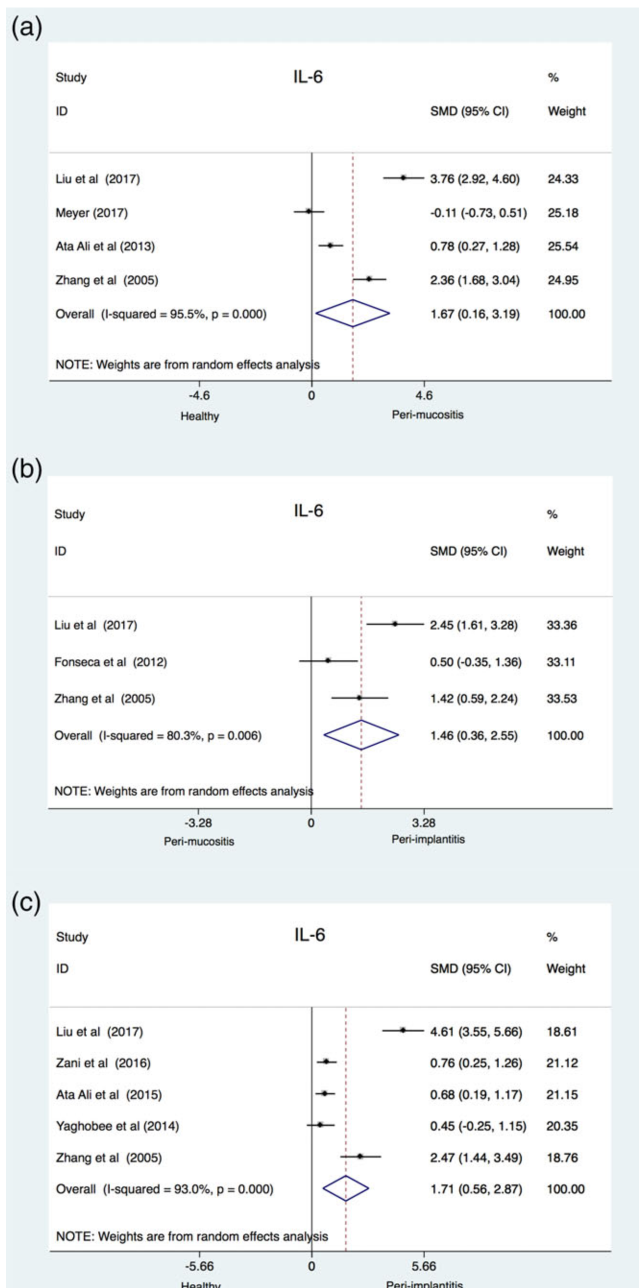

FIGURE 3 Forest plots presenting standard mean difference (SMD) of IL-6 comparing H with MU (A), MU with PI (B), and H with PI (C)

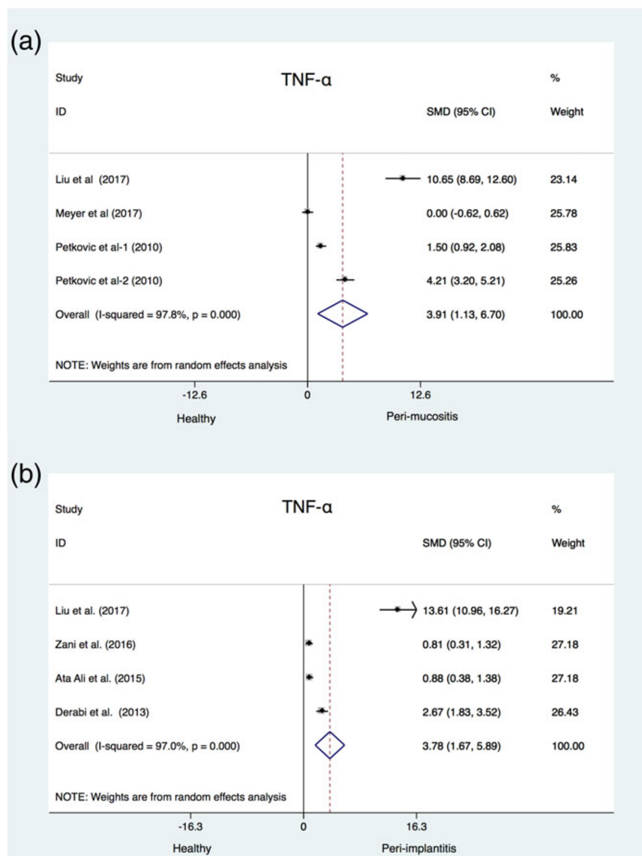

FIGURE 4 Forest plots presenting standard mean difference (SMD) of TNF-αcomparing H with MU (A), and (B) H with PI

in the comparison between H and PI (*P* = .013). Studies measuring IL-6 demonstrated no publication bias in all three comparisons (*P* = .234, .641, .08 respectively). Egger's test, combined with funnel plots, showed that for TNF-α, H versus MU (*P* = .067), as well as H versus PI groups (*P* = . 082) failed to prove the presence of publication bias.

4 | DISCUSSION

Peri-implant soft tissues demonstrate a strong inflammatory response to plaque accumulation; influencing the occurrence and development of peri-implant diseases; MU and PI.[11,22,43] Lipopolysaccharide in plaque directly stimulates macrophages, PMNs, and fibroblasts to produce proinflammatory cytokines and MMPs. These elicit an inflammatory response that overlaps bacterial action, inducing degenerative pathways of tissues; namely, an irreversible, rapid connective tissue destruction and an alteration of osteoclast and osteoblasts' activities.[12,17,37,44] Cytokines and MMPs are released in varying detectable amounts between different diseases and health conditions around implants; therefore, are recently investigated in the course of peri-implant diseases. In fact, IL-1β, IL-6, TNF-α, and MMP-8 are the most investigated biomarkers in literature.[9,27,43,49]

Inflammation continues to occur simultaneously with changes in clinical parameters around diseased implants, such as bleeding on probing; which indicates profuse bleeding and an increased amount of exudate around the implant. Accordingly, concentrations of the selected biomarkers from 19 studies showed an enhanced host response of PICF between health, MU, and PI. Their increased levels in PICF could facilitate an early diagnosis of peri-implant disease and prediction of its onset.[17,46] MMP-8 increased levels were previously associated with early implant failures.[47,48] One suggested reason is polymorphism in the promoter region of MMP-8. In this meta-analysis, early implant failure was supported by a marked increase in proinflammatory cytokines IL-1 β, IL-6, and TNF-α expressions between H and MU.

While the molecular mechanism is not fully comprehensible, it is illustrated that in the inflammatory stage of wound healing, IL-1β and TNF-α are chiefly responsible for prolonging plasminogen pathway of

clot lysis and propagating collagenase degradative pathway.[49] Some evidence suggests that IL-1β acts synergistically with TNF-α to initiate and propagate inflammation.[50] This is demonstrated by the robust levels of the three investigated cytokines in PI when compared to H, suggesting that they are indicative of the absence or presence of disease. Our data agree with Faot meta-analysis[19]; especially for IL-1 β and TNF-α. A correlation between pro-inflammatory cytokines and MMPs would suggest that they may cooperatively promote inflammation and tissue degradation in peri-implant diseases.[40,48] IL-1β and TNF-α induce the synthesis and secretion of MMP-8; which in turn, cleaves the triple helix of collagen and collectively degrade the extracellular matrix. The biomarkers' association to one another seem to be an added benefit supporting the choice of four in this review.

Interestingly, each cytokine showed a distinct pattern of shift from MU to PI. IL-1β levels increase, but not significantly between MU and PI. This may suggest that there is a "peak" response to enhanced IL-1β levels termed substrate saturation; that is, all receptor sites being fully occupied with IL-1β. Polymorphism in IL-1β gene expression could be another reason for varied responses between different individuals of the same disease category.[38,39] Contrary to IL-1β, IL-6 increases significantly between MU and PI (P = .009); suggesting that it may play a more important role in the non-linear pattern of bone loss occurring in PI.[51] IL-6 links innate to acquired immune responses; in which it induces differentiation of activated B cells in antibody-producing cells as well as naïve CD4 + T cells. It is conspicuous in chronic inflammation surrounding implants, leading to osteoclastic activation and peri-implant bone loss.[52–54] These correspond to the pattern of IL-6 increase in concentration between H and MU; H and PI.[33,55] To our knowledge, this is the first meta-analysis investigating IL-6 in H, MU, and PI. IL-6 was found to be more sensitive to severity of inflammation in peri-implant tissues.

Regarding TNF-α, there were insufficient studies to compare its level between MU and PI; therefore, meta-analysis could not be conducted. Further investigations are needed to comprehend its role in inflammation and in the progression of peri-implant diseases. In qualitative assessment of MMP-8, four out of five included articles showed MMP-8 being highly elevated in peri-implant diseases along with enhanced bleeding on probing and gingival index values. Specific and sensitive tests exist that facilitate accurate detection of MMP-8 in PICF.[11,16] MMP-8 shows a lot of potentials to be used in the progression of disease.[16,26] In contrast, Abo Youssef found that MMPs were not reliable indicators of implant health.

In this meta-analysis, a strict inclusion criterion featured clear definitions of H, MU, and PI. Unclear definitions were either lacking a specific definition, involving therapeutic intervention prior to assessment[47,56] or did not mention bone loss as the distinguishing parameter of MU from PI.[23] In the study of Panagakos,[39] MU was comprised of bone loss to a limit of 30%. MU was stringently defined as the absence of bone loss, so this study was excluded from MU. This criterion leads to a better distinction of disease and thus enables better judgment of biomarkers use.

While many methodological features of analysis were similar in the included studies, the functioning time of implants differed. This is a limitation to relating cytokine levels to the onset of peri-implant diseases. Similarly, publication bias was found in the comparison of IL-1β in H to PI. Results show high heterogeneity I^2 varying from 80.3% to 98.1%, which led to the use of the random effect model. Liu et al depict the highest heterogeneity in evaluation of IL-1β in all three conditions. One reason could be that cytokine levels were associated with high mobility group box 1 (HMGB1) protein increase as the principal investigated variable.[25] In other studies, the main reason for high heterogeneity could be attributed to the nature of studies, that is, the majority of included studies are cross-sectional. Alternatively, longitudinal peri-implant disease monitoring, combined with a non-treatment phase, could recognize a cluster of host response biomarkers associated with breakdown of tissues.[22,47,57,58]

Limited evidence exists to show the number of subjects with a sufficient sample size; that is, no calculations of statistical power were documented. Among the 19 included studies, only few studies accounted for smoking habits, although smoking has been identified as a risk indicator for peri-implant inflammation.[37,41,59,60] Other limitations include but are not limited to no consideration of other potential risk indicators for PI, such as history of periodontitis and tissue phenotype. Subsequently, biomarkers' concentrations could show marked discrepancy around implants with the same diagnosed implant disease.[35,61] Moreover, the type of protein assay used could affect the quality of results based on using different manufacturer products of ELISA and multiplex bead assays. Cytokine multiplex assays were found to be "comparable in sensitivity, accuracy, and reproducibility" to ELISA for the same analyte.[62] Concentration values followed a similar pattern among ELISA and bead assays but yielded different absolute cytokine concentrations. A trend of varied cytokine levels was expressed in this review.[63] In accordance with Khan's study, a trend is most important to monitor development and progression of disease. Finally, most studies lacked data on sensitivities and specificities to cytokines and time at which PICF samples were acquired; hence the probability of false positive or false negative results could not be calculated.

5 | CONCLUSION

Within the limitations of this study, pro-inflammatory cytokines in PICF, such as IL-1ß and IL-6, can be used as adjunct tools to clinical parameters to differentiate H from MU and PI. The results of this review indicate moderate evidence in literature to support the use of biomarkers with peri-implant diseases. A significant increase in IL-6 is shown between MU and PI while IL-1β levels did not increase as remarkably. Future research should focus more on longitudinal monitoring of biomarkers in order to deduce a suitable range in health and disease conditions.

ACKNOWLEDGMENTS

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TABLE 3 Risk of bias assessment

Criteria	Ata Ali et al	Meyer et al	Salvi et al	Teixeira et al	Zhang et al	Yaghobee et al	Panagakos et al	Kao et al	Aboyoussef et al	Liu et al	Ata Ali et al	Fonseca et al	Petkovic et al	Casado et al	Darabi et al	Zani et al	Wang et al	Janksa et al	Arakwa et al
Clearly stated research Q/objective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Defined study population	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Same populations/incl. and excl. prespecified	No/yes	Yes	Yes	No/yes	No/yes	Yes	No/yes	Yes	Yes	No/yes	No/yes	No/yes	No/yes	Yes	No/yes	No/yes	Yes	No/yes	No/yes
Sample size justification	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Exposure of interest measured prior to outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sufficient timeframe between exposure and outcome	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Exposure (categorical/Cont. Variable)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clearly defined exposure measures	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Exposure assessed more than once	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measures clearly defined/implemented consistently	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome assessors blinded to exposure status of participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Loss to follow-up 20% or less	NR	NR	NR	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confounding variable(s) measured and adjusted statistically	No	No	No	Yes	No	Yes	No	No	No	Yes	No	No	No	No	No	Yes	Yes	No	Yes
Conclusion "good/fair"	Good	Fair	Fair	Good	Fair	Good	Fair	Fair	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Fair	Fair

Abbreviations: excl., exclusion; incl., inclusion; NR, not recorded.

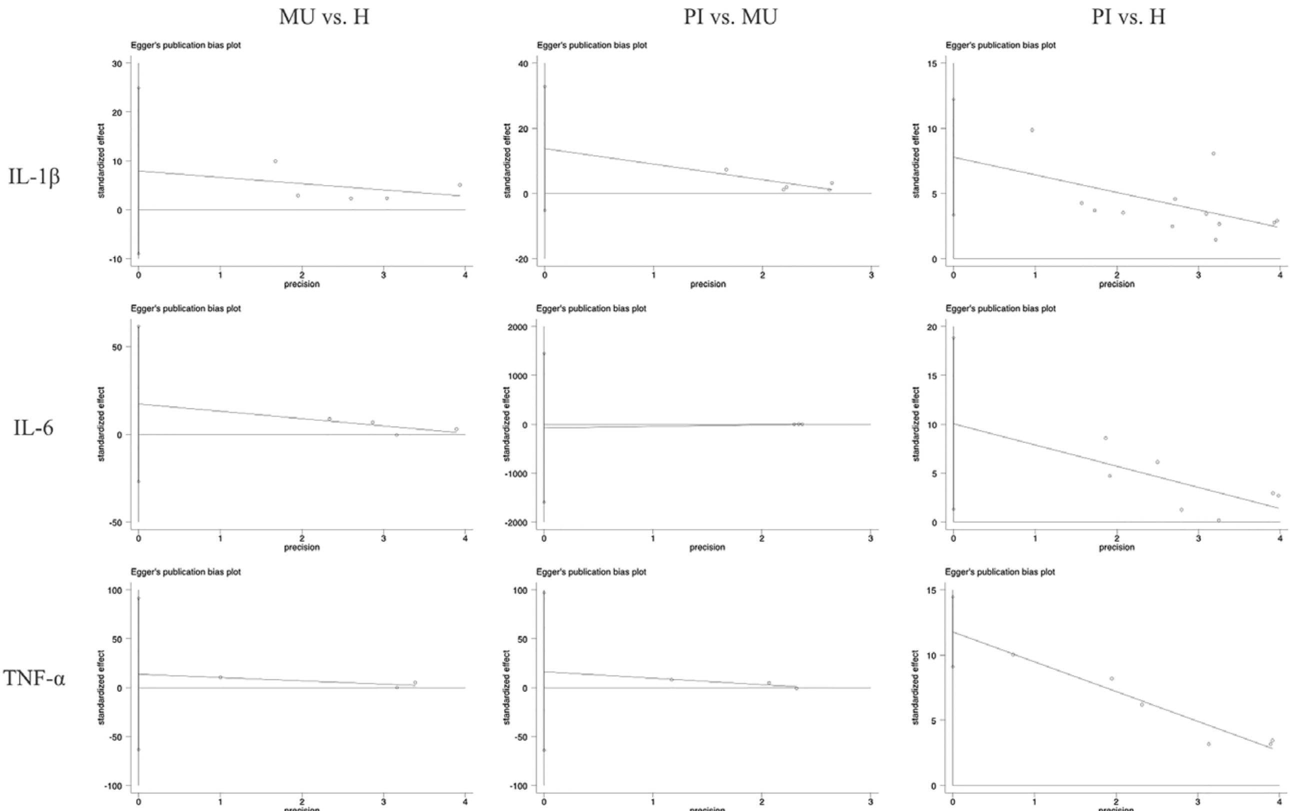

FIGURE A2 Egger linear plots assessing the public bias between studies

CONFLICT OF INTEREST

There was no conflict of interest declared. The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

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