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Original Article

Systemic Cytokine Alterations in Periodontitis Independent of Comorbidities: A Systematic Review and Meta-Analysis

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ABSTRACT: Systemic dissemination of inflammation-related proteins has been linked to unhealthy ageing and increased mortality. Yet, the systemic inflammatory profile of periodontitis, a common oral inflammatory disease, remains poorly characterised. The aim of this study was to evaluate the existing evidence linking alterations in serum levels of inflammation-related proteins to periodontitis. This study was registered in Prospero (CRD42024597308). The inclusion criteria were original, English language studies of human participants ≥16 years that assessed serum biomarkers in individuals with periodontitis and periodontally healthy controls. PubMed, Scopus, and Web of Science were searched on October 13, 2024, and complemented with a hand search. Two independent reviewers performed abstract screening, full-text assessment, risk-of-bias assessment (modified Newcastle-Ottawa Scale), and extraction of summary data. A random-effects meta-analysis was performed to estimate the ratio of mean protein (RoM) level between periodontitis cases and controls. From 9120 screened records, 206 studies were included in the qualitative data synthesis, yielding 17953 participants (157 unique proteins) in total. Data from 144 studies (39 proteins) were included in the meta-analysis. In individuals with periodontitis compared with controls, analyses showed significantly (P<0.05) higher levels of C-C motif chemokine ligand 2 (CCL2); interleukin (IL)-1β, IL-6, IL-17, IL-17A and IL-18; leptin; matrix metalloproteinase 8 (MMP-8), myeloperoxidase (MPO); receptor activator of nuclear factor kappa-B ligand (RANKL); and tumour necrosis factor α (TNF-α). Notably, CCL2, IL-1β, IL-6, IL-17, IL-17A, MMP-8, RANKL and TNF-α remained significantly elevated even in analyses restricted to systemically healthy participants, with additional significant associations observed for IL-12 and IL-33. Periodontitis is, independently of comorbidities, associated with systemic inflammation and with specific cytokines involved in metabolic and immune dysregulation, including inflammaging. These findings highlight the systemic impact of periodontitis and the importance of reducing the inflammatory burden to promote healthy aging and longevity.

Keywords: Periodontitis, systemic inflammation, serum, cytokines, inflammaging

INTRODUCTION

Inflammation is a vital biological response to infection or injury. Under physiological conditions, it is tightly regulated and self-limiting and plays a central role in preserving tissue integrity and maintaining homeostasis. Once a harmful stimulus is eliminated, inflammation will resolve, enabling tissue repair and functional recovery. By contrast, chronic or dysregulated inflammation can cause persistent, systemic dissemination of inflammatory mediators and feed a self-perpetuating loop of progressive tissue destruction. Systemic inflammation has been

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implicated in the development and progression of several chronic noncommunicable diseases, including cancer, metabolic-syndrome-related diseases, cardiovascular disease (CVD), autoimmunity, and neurodegeneration. Prolonged exposure to systemic inflammation is also associated with inflammaging, multi-organ frailty, and increased mortality [1, 2]. Identifying the precise triggers of systemic inflammation, which remain only partially understood, is therefore urgent.

Periodontitis is a common chronic inflammatory disease of the oral cavity. Moreover, it is linked to several systemic conditions characterised by chronic inflammation and immune dysregulation, such as cancer, CVD, type 2 diabetes, and rheumatoid arthritis (RA). Severe periodontitis affects approximately 10% of the global population, and results in tooth loss, impaired mastication, and reduced oral-health-related quality of life [3]. Disease onset usually occurs after 30 years of age, and periodontal tissue destruction accumulates throughout life, if uncontrolled. The disease is initiated by a dysbiotic shift in the subgingival commensal microbiota, which elicits an inflammatory immune response characterised by immune-cell recruitment and an imbalance in pro- and anti-inflammatory mediators [4]. These local inflammatory processes drive the progressive destruction of the periodontal ligament and alveolar bone. Moreover, locally produced inflammation-related proteins can disseminate from the periodontium to the circulatory system. Evidence indicates that local treatment of periodontitis ameliorates the systemic inflammatory load and specific surrogate markers of comorbid conditions. Previous meta-analyses have reported markedly elevated levels of C-reactive protein (CRP) in periodontitis patients that reverted after conventional periodontal treatment, i.e., mechanical removal of subgingival biofilm [5-7]. Moreover, studies of experimental disease models suggest that destructive inflammation in both periodontitis and arthritis is driven by maladaptive training of immune cells, elicited by increased levels of circulating inflammatory proteins [8]. This mechanism may explain why some individuals with periodontitis experience repeated disease recurrence despite receiving appropriate local treatment and maintaining good oral hygiene. Identifying circulating inflammatory proteins triggered by periodontitis could therefore enable identification of promising targets for precision intervention strategies in non-responders, while simultaneously reducing adverse effects on other organs and tissues.

Although numerous studies have evaluated the presence of serum inflammation-related proteins in periodontitis, the systemic serum cytokine profile remains inconclusive due to heterogeneity in study design, diagnostic criteria, and biomarker panels [5, 9-15]. No systematic review has comprehensively evaluated the relationship between periodontitis and a broad range of serum cytokines and inflammation-related proteins in adults. Through this systematic review and meta-analysis, we aim to synthesise and critically evaluate the available evidence linking periodontitis to alterations in the serum levels of cytokines and inflammation-related proteins.

MATERIALS AND METHODS

Protocol and registration

This review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16], and the protocol was registered in PROSPERO (CRD42024597308). Identified studies were imported into Covidence for management of the different stages of the review.

Eligibility criteria

The main inclusion criteria were studies that quantitatively compared the serum levels of inflammatory proteins in human periodontitis cases and periodontally healthy controls, aged 16 years and older. The clinical signs of periodontitis include gingival inflammation, the formation of deepened periodontal pockets, and the presence of alveolar bone loss. Diagnosis is performed through a clinical examination of the periodontium with a periodontal probe and by radiographic imaging. The current disease definition is based on the presence of clinical attachment loss (i.e., breakdown of periodontal tissues) in at least two non-adjacent teeth. Subsequent staging (I-IV) describes the severity and extent of periodontal damage [17]. Therefore, only studies that clearly stated that their cases fulfilled this criterion or included a similar stage of periodontitis based on previous disease classifications were included [18, 19]. Studies relying solely on self-reported periodontitis or the Community Periodontal Index of Treatment Needs (CPITN), which is intended for periodontal screening and not for diagnostics, were excluded. Individuals showing no signs of attachment loss were categorised as periodontally healthy controls and served as the comparison group.

The inflammatory proteins included in this study were cytokines, chemokines, adipokines, growth factors, matrix metalloproteinases (MMPs), bone turnover proteins, adhesion molecules, complement fragments, and prostaglandins. Data for different oligomeric states of the same protein were merged and presented as data for the single protein. However, for the interleukin (IL)-17 family, which consists of different members with diverse biological functions, data for each member (IL-17A-F)

were extracted and presented separately from data for which only the family name IL-17 was used. In addition to the subgroups of proteins named above, specific proteins deemed related to inflammation, for example some proteases, glycoproteins, neuropeptides, heat shock proteins and different soluble cluster of differentiation proteins were included. Acute-phase proteins, such as CRP and fibrinogen were not included, as several up-to-date systematic reviews already exist for these proteins [6, 7]. However, CRP was included in the search to ensure that no relevant studies were missed, as CRP is commonly investigated alongside other proteins. Analytes including genetic material (e.g. cytokine mRNA), antibodies against bacteria, autoantibodies, immunoglobulins, triglycerides lipids, glycosylated haemoglobin, blood glucose, vitamins, or ions were considered beyond the scope of this review. Studies that presented data derived from plasma samples instead of serum were excluded to enable comparability of the included studies. Furthermore, studies designed to evaluate periodontitis in the presence of another concomitant comorbidity or condition (e.g. pregnancy, systemic disease or obesity) were excluded, although partial data were extracted from a systemically healthy case group when available. In cases of missing data, the study authors were not contacted, and studies were excluded if no protein concentrations were presented.

All original studies that had been published and subjected to peer review were eligible for inclusion. Review articles, non-empirical studies, case reports, letters to the editor, and articles in languages other than English were excluded.

Search strategy

A comprehensive literature search that included all published articles up until 13th of October 2024 was conducted using PubMed, Scopus and Web of Science and complemented by a hand search of reference lists in relevant articles (Supplementary Table 1). A search strategy for PubMed was developed with an information technician and included a combination of medical subject headings (MeSH) and free-text terms related to periodontitis, inflammation-related proteins, and serum. Duplicate articles were automatically removed in Covidence prior to screening. Grey literature was not searched.

Study selection

After duplicate removal, two independent reviewers (M.W. and K.H.M.) screened all titles and abstracts for eligibility. Additional duplicates identified during screening were excluded. Studies selected for inclusion by at least one reviewer during abstract screening were advanced to full-text assessment. Full texts were assessed independently by two reviewers (M.W. and E.K.), and disagreements were resolved by discussion with a third reviewer (P.L.).

Data extraction

Data were extracted independently by two reviewers (M.W. and E.K.) using a predefined template in Covidence. Discrepancies were resolved through discussion or by consultation with a third reviewer (P.L.) if needed. The extracted data included (i) information on the study characteristics (title, author, publication year, and study design); (ii) inclusion and exclusion criteria; (iii) participant demographics (age, sex, smoking habits, case definition for periodontitis, including subgroups as defined in the article); (iv) protein analysis method; and (v) the outcome (serum protein concentrations in periodontitis cases and periodontally healthy controls). For interventional studies that assessed serum proteins at several time points, only baseline data were extracted. Serum protein levels for females and males respectively were not extracted as most studies presented summary data for cases (periodontitis or periodontitis subgroups) and controls. The serum protein concentrations were directly extracted from the results section (tables, text, or figures). The primary outcomes were the mean and standard deviation (SD). In addition, all other reported summary measures, such as median, quartiles, minimum, maximum, and confidence intervals (CI) were extracted when available. The software Web Plot Digitizer (https://automeris.io) was used to extract protein levels when protein concentrations were only presented graphically.

Quality assessment

The risk of bias in all included articles was assessed by two independent reviewers (M.W. and E.K.) using a modified version of the Newcastle-Ottawa scale (NOS) tailored for cross-sectional studies, as only cross-sectional data were extracted (Supplementary Table 2) [20]. The scale evaluated the domains of selection, comparability, and outcome. Disagreements were resolved by consensus. Each article was assessed on a 0–10 star scale; based on the total score, studies were categorised as unsatisfactory (0–4 stars), satisfactory (5–6 stars), good (7–8 stars), or very good (9–10 stars).

Statistical analysis

A descriptive synthesis was created that included summary tables and a comparison of the study findings.

For studies presenting data on separate subgroups, the mean and SD for a combined group were calculated [21]. In some studies (14.6%) median values along with quartiles, and/or minimum or maximum values were reported. The mean and SD were then estimated using the quantile estimation method for sample sizes ≥30 and the Box–Cox method for sample sizes <30, considering the skewed distribution of protein levels. As these values were derived through statistical approximation, the estimation process may introduce additional uncertainty in the pooled estimates [22]. For each protein reported in ≥3 studies with sufficient statistical data, a random-effects meta-analysis was conducted to obtain summary effect estimates.

The ratio of means (RoM) was used as the summary effect size, reflecting the relative difference in biomarker levels between individuals with periodontitis and controls, as it is less sensitive to variations in methods of serum analysis. No cut-offs for interpreting RoM values were used because no validated thresholds exist and their clinical meaning depends on the specific outcome. Each study's RoM was log-transformed and then pooled using the inverse-variance method under a random-effects model. The pooled estimate and its CIs were then exponentiated to return the results to the original ratio scale. The between-study variance (τ^2) was estimated using a restricted maximum likelihood estimator, and the Hartung–Knapp adjustment was applied to estimate the CI of the pooled effect. Heterogeneity was assessed using Cochran's Q and the I^2 statistic.

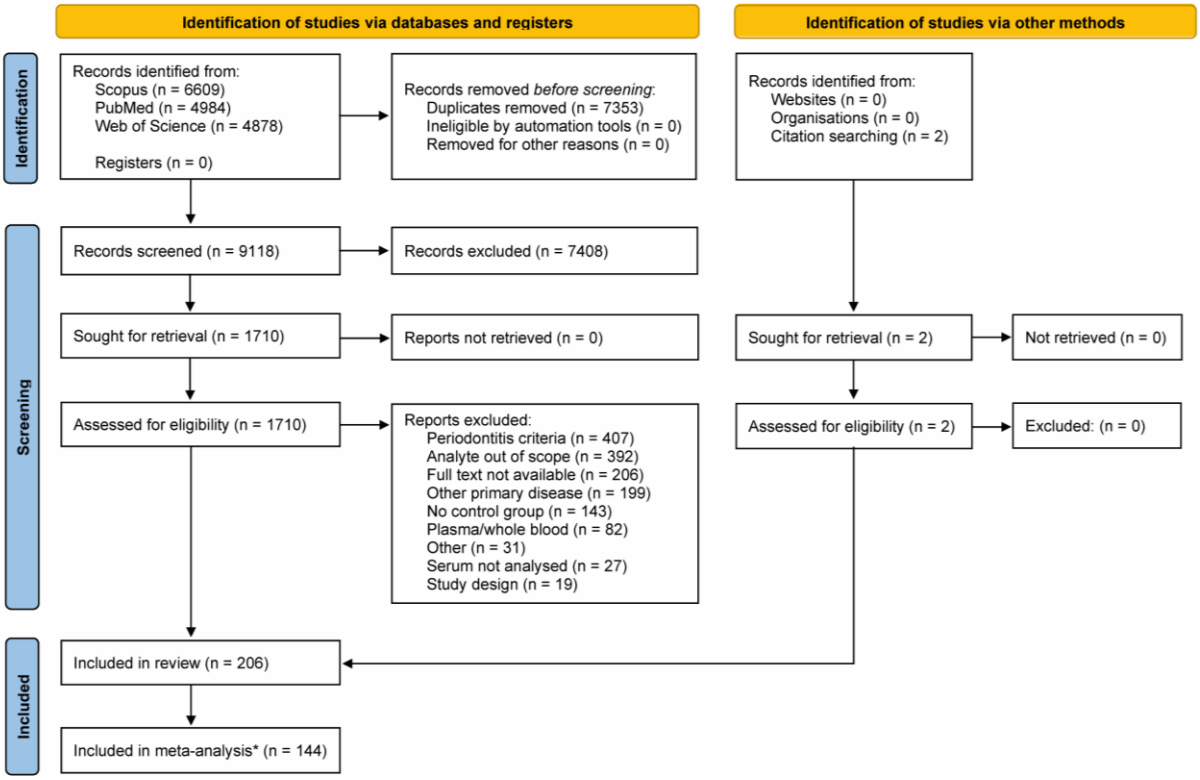

Figure 1. PRISMA flowchart of the study selection. *Meta-analysis was conducted for proteins for which sufficient data was reported in at least three studies.

In addition, a 95% prediction interval was calculated to estimate the expected range of RoM in future studies. For proteins that were included in at least 10 studies, potential publication bias was evaluated using Egger's test. To explore potential sources of heterogeneity, subgroup analyses were performed by restricting the analysis to studies that either only included systemically healthy participants or to studies with non-smoking cases and controls. Since only a subset of studies contributed to each subgroup, subgroup analyses were performed only when ≥3 studies met the subgroup criterion. To qualify as including only systematically healthy participants, studies had to clearly state in their inclusion or exclusion criteria that participants with any other (self-reported) systemic disease were excluded (e.g., "The study included only systemically healthy individuals"). Stratification by method, geographic region, sex, and age was considered but deemed inappropriate due to the low granularity and overall characteristics of the available data. The influence diagnostics and leave-one-out analyses were performed

for proteins with at least 10 studies to evaluate the impact of individual studies on the pooled estimates.

All statistical analyses were conducted using the software R, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria) with the meta package (v. 7.0-0), metafor package (v. 4.8-0), and dmetar package (v. 0.1.0). Statistical significance was defined as $P < 0.05$.

RESULTS

The literature search identified 16471 studies, of which 4984 were from PubMed, 6609 were from Scopus, and 4878 were from Web of Science. Two additional studies were identified by hand searching. After the removal of 7353 duplicates, 9120 studies remained for title and abstract screening. Of these, 1712 studies were deemed eligible for full-text review. A total of 1506 studies were removed in the full-text review, resulting in the inclusion of 206 studies (Supplementary Table 3); of these, proteins from 144 studies were included in the meta-analysis (Fig. 1). The most common reasons for exclusion were not fulfilling the established criteria for periodontitis, analytes outside the scope of the study, and full text not available or not in English (Fig. 1). All records excluded during the full-text review and the reasons for exclusion are presented in Supplementary Table 4.

Table 1. Descriptive table of included studies with demographic information. Significantly altered proteins are bolded.

Ref.	Author, Year	Country	Classification	Definition	Female cases n (%)*	Female controls n (%)*	Age, cases Mean, SD*	Age control, Mean, SD*	Smokers Cases n (%)*	Smokers control n (%)*	Analysis method	Analyte±
1	Abdul-Wahab 2024	Iraq	AAP/EFP 2017	CP	50 (22)	50 (28)	43.7, 4.5	41.8, 6.4	0 (0)	0 (0)	NS	**IL-33** ↑
2	Abuhussein 2014	USA	Own/modified	CP	49 (49)	8 (88)	NS	NS	20 (41)	1 (13)	ELISA	sFas, sFasL
3	Acharya 2015	India	Own/modified	CP	15 (NS)	15 (NS)	30-55[a]	30-55[a]	0 (0)	0 (0)	ELISA	**IL-10** ↓
4	Acharya 2016	India	Own/modified	CP	20 (NS)	20 (NS)	30-55[a]	30-55[a]	0 (0)	0 (0)	ELISA	**IL-4** ↓, **IL-6** ↑, **TNF-α** ↑
5	Acharya 2019	India	Own/modified	CP	15 (53)	15 (47)	45.9, 6.7	43.7, 5.0	0 (0)	0 (0)	ELISA	**sTWEAK** ↓
6	Acharya 2022	UAE	AAP/EFP 2017	CP	15 (60)	15 (53)	43.7, 7.2	40.3, 8.1	0 (0)	0 (0)	ELISA	**CXCL-2** ↓
7	Acharya 2024	UAE	AAP/EFP 2017	Stage II-III	15 (40)	15 (47)	42.3, 4.7	44.6, 3.9	0 (0)	0 (0)	ELISA	**CXCL-16** ↓
8	Ahuja 2019	India	AAP 1999	CP	30 (NS)	30 (NS)	NS	NS	0 (0)	0 (0)	ELISA	**Leptin** ↑
9	Al-Kubaisi 2024	Iraq	AAP/EFP 2017	Stage I-IV	50 (20)	50 (20)	40.1, 6.4	40.1, 6.4	31 (62)	0 (0)	ELISA	**suPAR** ↑
10	Al-Obaidi 2023	Iraq	Own/modified	P	30 (47)	25 (56)	38.5, 7.5	36.9, 6.5	NS	NS	ELISA	NLRP3, **IL-18** ↑
11	Albandar 2002	USA	AAP 1989	EOP	83 (NS)	92 (NS)	19-25[a]	19-25[a]	NS	NS	RIA	IL-1β
12	Aldahlawi 2018	SA	Own/modified	CP	31 (65)	25 (80)	31.7, 18-59[b]	27.8, 18-48[b]	6 (19)	0 (0)	ELISA	**CXCL-10** ↑
13	Aldahlawi 2019	SA	Own/modified	P	30 (63)	13 (100)	31.7, 11.0	27.8, 7.0	6 (20)	0 (0)	ELISA	**RANKL** ↑, **OPG** ↑
14	Alkan 2019	Turkey	AAP 1999	CP	15 (53)	15 (53)	36.3, 1.6	35.1, 2.5	0 (0)	0 (0)	ELISA	FOLR1
15	Anil 2013	SA	AAP 1999	CP	60 (NS)	30 (NS)	34.7, 7.9	34.5, 6.2	30 (50)	0 (0)	ELISA	**MCP-1** ↑
16	Anumala 2016	India	AAP 1999	CP	20 (NS)	20 (NS)	37.6, 9.9	20.6, 2.0	NS	NS	ELISA	**RANTES** ↑
17	Arief 2017	Malaysia	Own/modified	CP	28 (43)	27 (89)	45.3, 13.0[c]	33.0, 8.0[c]	0 (0)	0 (0)	ELISA	**IL-17** ↑
18	Arikan 2023	Turkey	AAP/EFP 2017	Stage IIIC	40 (43)	20 (60)	NS	30.5, 27-33.5[c]	20 (50)	0 (0)	ELISA	**RANKL** ↑□, OPG, IL-34

19	Arvikar 2021	USA	AAP 1999	CP	20 (50)	20 (85)	53, 24-68[c]	46, 28-63[c]	1 (5)	0 (0)	BBIA	> 4 analytes ♦
20	Ata 2023	Turkey	Own/modified	CP	15 (40)	15 (47)	47, 8	45, 6	0 (0)	0 (0)	ELISA + EL	**CTRP3 ↑,** Procalcitonin
21	Awang 2014	UK	Own/modified	P	97 (NS)	77 (NS)	47, 8	38, 12	0 (0)	0 (0)	ELISA	IL-17A-F, IL-17AF♦
22	Ay 2012	Turkey	AAP 1999	AP, CP	37 (54)	20 (60)	NS	NS	0 (0)	0 (0)	ELISA	OB, s-OBR
23	Babu 2017	India	AAP 1999	CP	20 (NS)	20 (NS)	23-53[a]	23-53[a]	NS	NS	ELISA	**MCP-1 ↑**
24	Balci 2021	Turkey	AAP/EFP 2017	Stage IIIB	20 (65)	20 (60)	37.6, 12.3	33.7, 8.6	0 (0)	0 (0)	ELISA	CX3CL, **CX3CR1 ↓** IL-1β
25	Balli 2015	Turkey	Own/modified	CP	30 (50)	20 (50)	41.2, 5.4	37.8, 4.8	0 (0)	0 (0)	ELISA	Periostin
26	Baltacıoğlu 2014	Turkey	AAP 1999	CP, GAgP	60 (53)	28 (54)	29.9, 5.7	28.1, 4.0	0 (0)	0 (0)	ELISA	**RANKL ↑, OPG ↓**
27	Bawankar 2018	India	AAP 1999	CP	50 (NS)	25 (NS)	30-65[a]	30-65[a]	25 (50)	0 (0)	ELISA	**IL-1β ↑**
28	Bostanci 2013	Turkey	AAP 1999	CP, GAgP	43 (58)	20 (30)	39.3, 8.3	36.0, 2.6	14 (33)	4 (20)	ELISA	**sTREM-1 ↑**
29	Bostanci 2017	Turkey	AAP 1999	CP	15 (73)	10 (70)	32.80, 8.6	34.0, 6.9	0 (0)	0 (0)	ELISA	**IL-1β ↑, IL-1RA, IL-10 ↑**
30	Boström 2015	Sweden	Own/modified	P	43 (47)	41 (61)	55.3, 51.9-58.7[d]	44.6, 42.3-46.9[d]	NS	NS	BBIA	> 4 analytes ♦
31	Caribé 2020	Brazil	Own/modified	P	40 (NS)	38 (NS)	58.2, 7.4	59.1, 9.4	0 (0)	0 (0)	ELISA	SIRT1, MBL
32	Caribé 2020	Brazil	Own/modified	P	20 (NS)	20 (NS)	54.2, 4.8	56.5, 6.7	0 (0)	0 (0)	ELISA	SIRT1, MBL
33	Cekici 2023	Turkey	AAP/EFP 2017	Stage III	20 (50)	20 (55)	39.7, 7.6	32, 7.4	0 (0)	0 (0)	ELISA	**SIRT6 ↓**, LXA4
34	Cetinkaya 2013	Turkey	AAP 1999	CP	16 (38)	16 (50)	44.0, 7.0	28.6, 6.2	0 (0)	0 (0)	ELISA	IL-1β, IL10
35	Cetin Özdemir 2022	Turkey	AAP/EFP 2017	Stage III	22 (36)	26 (69)	38.4, 7.0	35.5, 8.5	0 (0)	0 (0)	Other	Procalcitonin
36	Chang 2020	USA	AAP 1999	CP	9 (33)	10 (50)	52.2, 10.8	52.8, 9.2	0 (0)	0 (0)	ELISA	IL-1β, IL-6, TNF-α
37	Chaturvedi 2015	India	CDC/AAP 2007	P	40 (NS)	20 (NS)	41.1, 8.8	39.5, 9.0	0 (0)	0 (0)	ELISA	**sCD40L↑** □
38	Cheah 2020	Malaysia	CDC/AAP 2007	CP	30 (50)	15 (80)	39.5, 24[e]	34, 20[d]	4 (13)	2 (13)	ELISA	**LL-37 ↑**
39	Chen 2010	China	Own/modified	P	25 (52)	24 (58)	23-52[a]	22-53[a]	0 (0)	0 (0)	ELISA	**PAF ↑**
40	Cheng 2018	UK	Own/modified	CP, AP	30 (50)	13 (54)	NS	NS	NS	NS	BBIA	> 4 analytes
41	Cicmil 2023	Bosnia	AAP 1999	P	39 (59)	39 (62)	36.2, 3.5	35.6, 3.0	8 (21)	11 (28)	BBIA + ELISA	> 4 analytes ♦
42	Cifcibasi 2015	Turkey	AAP 1999	GAP	19 (63)	22 (64)	28.8, 4.1	25.9, 5.7	0 (0)	0 (0)	ELISA	IL-17 ↑, IL-23 ↑, MPO ↑
43	D'Aiuto 2010	UK	AAP 1999	P	145 (52)	56 (50)	47.3, 8.3	46.4, 7.4	44 (30)	18 (32)	ELISA	IL-6
44	Davies 2011	UK	AAP 1999	AgP	30 (63)	30 (63)	36.7, 6.3	36.3, 6.4	7 (23)	5 (17)	ELISA + SMSIA	> 4 analytes
45	De Alencar 2020	Brazil	AAP/EFP 2017	Stage II-III	30 (NS)	8 (NS)	NS	NS	0 (0)	0 (0)	BBIA	> 4 analytes
46	Detzen 2017	USA	Own/modified	P	70 (47)	70 (40)	43.2, 9.6	42.4, 10.2	0 (0)	0 (0)	ELISA	**sCD163 ↑**
47	Devanoorkar 2012	India	AAP 1999	CP	20 (NS)	20 (NS)	20-50[a]	20-50[a]	0 (0)	0 (0)	ELISA	Resistin
48	Dhulipalla 2023	India	AAP 1999	GCP	32 (NS)	32 (NS)	43.7, 9.2	42.2, 6.4	0 (0)	0 (0)	ELISA	**TNF-α ↑**

49	Ding 2022	China	AAP/EFP 2017	CP	29 (62)	20 (50)	51.5, 9.1	43.4, 15.9	0 (0)	0 (0)	ELISA	**IL-6** ↑
50	Dopico 2023	Spain	CDC/AAP 2007	P	30 (23)	30 (23)	47.9, 7.5	47.9, 6.3	0 (0)	0 (0)	ELISA	**IL-6** ↑, **cFN** ↑, HSP60
51	Duarte 2010	Brazil	AAP 1999	GAgP, GCP	28 (50)	14 (50)	35.3, 8.8	26.6, 4.3	0 (0)	0 (0)	ELISA	**TNF-α** ↑□, **IL17** ↑□
52	Duzagac 2016	Turkey	AAP 1999	CP	15 (53)	15 (60)	41.1, 7.1	39.7, 6.5	0 (0)	0 (0)	ELISA	IL-6, **IL-10** ↓, TNF-α, **Adiponectin** ↓
53	Dyab 2024	Sweden	Own/modified	P	42 (45)	38 (71)	54.0, 46.8-63.3[e]	44.0, 37.0-51.0[e]	30 (71)	10 (26)	ELISA	**BAFF** ↑
54	Eldzharov 2021	Russia	AAP/EFP 2017	GCP	40 (NS)	40 (NS)	49.2, 4.3	49.7, 4.8	0 (0)	0 (0)	ELISA	> 4 analytes ♦
55	Ersahan 2023	Turkey	AAP/EFP 2017	Stage I-IV	42 (52)	40 (45)	44.0, 9.8	39.9, 13.1	0 (0)	0 (0)	ELISA	**MR-proADM** ↑, **IL-12** ↑, **TNF-α** ↑
56	Fentoğlu 2011	Turkey	AAP 1999	CP	28 (NS)	20 (NS)	31-54[a]	31-54[a]	0 (0)	0 (0)	ELISA	TNF-α, IL-1β, IL-6
57	Gao 2021	China	AAP 1999	Stage III-IV	32 (56)	43 (65)	52.3, 9.8	53.0, 9.8	3 (9)	7 (16)	ELISA	**Calciprotectin** ↑
58	George 2013	India	Own/modified	CP	25 (40)	20 (40)	30-60[a]	30-60[a]	0 (0)	0 (0)	ELISA	**IL-6** ↑
59	Gundala 2014	India	Own/modified	CP	30 (NS)	30 (NS)	44.9, 9.1	48.3, 6.6	NS	NS	ELISA	**Leptin** ↑
60	Gunpinar 2020	Turkey	AAP/EFP 2017	P	20 (60)	20 (75)	44.8, 8.4	32.8, 10.3	0 (0)	0 (0)	ELISA	**Netrin-1** ↓, **Unc5b** ↓
61	Gupta 2015	India	CDC/AAP 2007	CP	30 (NS)	15 (NS)	NS	NS	0 (0)	0 (0)	ELISA	**sCD40** ↑, **MCP-1** ↑
62	Gül 2024	Turkey	AAP/EFP 2017	Stage IIIB	35 (43)	35 (46)	56.2, 8.4	55.4, 8.52	0 (0)	0 (0)	ELISA	**Asprosin** ↑
63	Gül 2024	Turkey	AAP/EFP 2017	P	35 (NS)	30 (NS)	38.2, 7.0	33.6, 11.4	0 (0)	0 (0)	ELISA	**Asprosin** ↑
64	Gümüş 2014	Turkey	AAP 1999	AgP, CP	45 (51)	20 (50)	42.4, 8.4	36.1, 6.6	18 (40)	7 (35)	ELISA	> 4 analytes ♦
65	Görgülü 2022	Turkey	AAP/EFP 2017	Stage IIIB-C	45 (47)	20 (55)	NS	NS	0 (0)	0 (0)	ELISA	MMP-8, MAF, MIP-1α ↑□, **M-CSF** ↑
66	Habeeb 2021	Iraq	Own/modified	P	60 (37)	28 (57)	41.8, 12.5	40.7, 12.4	0 (0)	0 (0)	ELISA	IL-33
67	Hamad 2022	Iraq	AAP/EFP 2017	P	25 (NS)	13 (NS)	36-66[a]	36-66[a]	0 (0)	0 (0)	ELISA	**MCP-1** ↑
68	Hamad 2022	Iraq	AAP/EFP 2017	P	25 (NS)	13 (NS)	36-66[a]	36-66[a]	0 (0)	0 (0)	ELISA	**suPAR** ↑
69	Hameed 2023	Iraq	AAP/EFP 2017	P	20 (25)	10 (60)	51.0, 7.6	43.7, 8.7	0 (0)	0 (0)	ELISA	**Procalcitonin** ↑
70	Han 2021	China	AAP 1999&2017	AgP, Stage III-IV	98 (79)	103 (64)	26.2, 5.1	30.4, 10.2	0 (0)	0 (0)	ELISA	**IL-6** ↑
71	Han 2023	China	AAP/EFP 2017	P	60 (53)	60 (57)	33.3, 5.5	31.0, 6.5	0 (0)	0 (0)	ELISA	**IL-6** ↑
72	Haririan 2016	Austria	AAP 1999	AgP, CP	56 (36)	44 (52)	NS	35.4, 10	15 (27)	7 (16)	ELISA	**MRP-8/14** ↑
73	Hayashi 1999	Japan	Own/modified	P, EOP	38 (NS)	25 (NS)	16-65[a]	20-34[a]	NS	NS	ELISA	**sCD14** ↑
74	Haytural 2015	Turkey	Own/modified	CP	30 (33)	20 (55)	40.5, 5.3	32.5, 3.0	20 (67)	NS	BBIA	MCP-1, RANTES, **MIP-1a** ↓□, **MIP-1b** ↑□
75	Hendek 2019	Turkey	Own/modified	CP	40 (73)	40 (53)	38.5, 7[e]	36, 6[e]	0 (0)	0 (0)	ELISA	**MCP-1** ↑
76	Hetta 2020	Egypt	AAP/EFP 2017	Stage II	55 (42)	20 (35)	37.5, 4.2	35.7, 1.6	0 (0)	0 (0)	ELISA	> 4 analytes ♦
77	Ikbal 2023	India	Own/modified	P	20 (NS)	20 (NS)	25-60[a]	25-60[a]	0 (0)	0 (0)	ELISA	**IL-10** ↓

78	Isola 2021	Italy	AAP/EFP 2017	P	40 (53)	38 (50)	52, 48-55[e]	51, 47-54[e]	3 (8)	1 (3)	ELISA	**ET-1 ↑, Galectin-3 ↑**
79	Isola 2021	Italy	Own/modified	P	31 (52)	31 (48)	53, 48-58[e]	52, 47-57[e]	3 (10)	2 (6)	ELISA	MMP-9
80	Isola 2022	Italy	AAP/EFP 2017	Stage IIB	34 (47)	32 (47)	52, 1.9	51, 2.1	1 (3)	1 (3)	ELISA	NLRP, **IL-1β ↑, Caspase-1 ↑**
81	Jain 2020	India	AAP 1999	CP	20 (NS)	20 (NS)	24-60[a]	24-60[a]	NS	NS	ELISA	**TNF-α ↑**
82	Jaradat 2013	Germany	AAP 1999	CP	136 (49)	91 (52)	46.3, 9.7	46.1, 9.4	0 (0)	0 (0)	ELISA	**hBD-2 ↓**
83	Jentsch 2017	Germany	AAP 1999	CP	15 (87)	15 (80)	46.7, 14.7	37.2, 12.6	0 (0)	0 (0)	ELISA	Total Ghrelin, **chemerin ↑**
84	Kabacaoğlu 2024	Turkey	AAP/EFP 2017	Stage IIIB-C	15 (53)	15 (73)	37, 20-58[c]	27, 25-32[c]	0 (0)	0 (0)	ELISA	> 4 analytes ♦
85	Kaiser 2018	UK	Own/modified	AgP	30 (70)	28 (68)	35.5, 5.0	39.4, 11.2	14 (47)	3 (11)	ELISA	> 4 analytes ♦
86	Kalra 2013	India	Own/modified	CP	15 (47)	10 (50)	32.2, 3.9	32.7, 3.7	0 (0)	0 (0)	ELISA	**SCF ↑**
87	Karthikeyan 2007	India	Own/modified	CP	14 (NS)	14 (NS)	30-39[a]	30-39[a]	0 (0)	0 (0)	ELISA	**Leptin ↑**
88	Keles Yucel 2020	Turkey	AAP/EFP 2017	Stage III	40 (48)	23 (52)	37.9, 6.1	36.4, 5.8	0 (0)	0 (0)	IFMA	**aMMP-8 ↑**
89	Keles Yucel 2022	Turkey	AAP/EFP 2017	Stage IIIC	50 (50)	25 (48)	38, 26-49[c]	35, 25-45[c]	0 (0)	0 (0)	ELISA	**TFF-1 ↑, IL-1β ↑, TFF-3 ↑**
90	Khalaf 2014	Sweden	Own/modified	P	30 (57)	30 (57)	54.5, 31-74[b]	55.2, 27-74[b]	12 (40)	0 (0)	ELISA	CXCL-8, TGF-b1, IL-2
91	Khalid 2017	India	AAP 1999	CP	24 (NS)	20 (NS)	30-50[a]	30-50[a]	0 (0)	0 (0)	ELISA	**ET-1 ↑**
92	Khan 2020	India	AAP 1999	CP	20 (55)	20 (50)	38.8, 7.8	31.0, 7.6	0 (0)	0 (0)	ELISA	**OSM ↑**
93	Kobayashi 2016	Japan	AAP 1999	CP	25 (56)	20 (60)	64.3, 1.4	65.4, 2.2	0 (0)	0 (0)	ELISA	IL-6
94	Korkmaz 2024	Turkey	AAP/EFP 2017	P	30 (67)	30 (70)	42.9, 10.3	27.3, 6.7	0 (0)	0 (0)	ELISA	**MMP-9 ↑, IL-38 ↑, IL-17 ↑, IL-36γ ↑**
95	Kriaučiūnas 2022	Lithuania	AAP/EFP 2017	Stage I-III	201 (58)	500 (50)	70, 16[e]	66, 15[d]	0 (0)	0 (0)	ELISA	SIRT1
96	Kriauciunas 2024	Lithuania	AAP/EFP 2017	Stage III-IV	40 (NS)	40 (NS)	NS	NS	0 (0)	0 (0)	ELISA	VEGFA
97	Kumar 2019	India	Own/modified	CP	10 (70)	10 (60)	38.6, 6.5	25.4, 1.6	0 (0)	0 (0)	ELISA	YKL40
98	Kumari 2014	India	Own/modified	CP	15 (53)	10 (50)	32.1, 4.2	31.8, 4.9	0 (0)	0 (0)	ELISA	**MCP-4 ↑**
99	Kurgan 2022	Turkey	AAP/EFP 2017	Stage IIIB	20 (45)	20 (60)	41.6, 10.8	39.6, 6.7	0 (0)	0 (0)	ELISA	IL-6
100	Latorre Uriza 2024	Colombia	AAP/EFP 2017	Stage III-IV	30 (47)	45 (62)	55.1	43.9	0 (0)	0 (0)	BBIA	> 4 analytes
101	Leira 2018	Spain	Eke classification	P	40 (40)	40 (35)	43.8, 10.3	42.0, 11.7	10 (25)	7 (18)	ECL	**NT-proBNP ↑**
102	Leira 2018	Spain	Eke classification	CP	19 (100)	37 (92)	48.0, 10.9	43.3, 9.9	5 (26)	5 (14)	ECL	Procalcitonin
103	Leira 2019	Spain	CDC/AAP 2007	CP	26 (NS)	51 (NS)	NS	NS	NS	NS	ELISA	**IL-6,↑, IL-10 ↓, CGRP ,↑**

104	Leira 2020	Spain	Eke classification	P	75 (35)	75 (35)	44.8, 10.3	44.7, 12.2	11 (15)	7 (9)	ELISA	**IL-6,↑, Ab42:40 ,↑, Ab1-40 ,↑, Ab1-42 ,↑**
105	Leira 2021	UK	Own/modified	P	50 (68)	50 (50)	43, 9	43, 9	0 (0)	0 (0)	ELISA	**sTREM-1↑**
106	Li 2012	China	AAP 1999	CP	122 (6)	532 (44)	54.4, 7.8	36.9, 9.7	113 (93)	521 (98)	ELISA	> 4 analytes ♦
107	Liao 2011	China	AAP 1999	CP	40 (40)	108 (44)	49.5, 9.8	36.5, 3.5	0 (0)	0 (0)	ELISA	**MMP-2 ↑, GM-CSF ↑, TIMP-1 ↑, IL-12 ↑**
108	Ligade 2023	India	Own/modified	P	10 (50)	10 (50)	41.2	32.3	0 (0)	0 (0)	ELISA	Adipolin
109	Lin 2024	China	Own/modified	P	58 (50)	28 (54)	61.2, 7.7	61.9, 11.8	6 (10)	0 (0)	ELISA	**IL-33 ↓**
110	Lobão 2019	Brazil	Own/modified	CP	33 (61)	29 (62)	41.1, 7.8	39.6, 9.0	0 (0)	0 (0)	ELISA	IL-6
111	Lobo 2019	India	AAP 1999	CP	40 (NS)	40 (NS)	34.6	33.7	NS	NS	ELISA	**MMP-7 ↑**
112	Lokhande 2019	India	Own/modified	CP	30 (NS)	16 (NS)	31.5, 4.3	36.6, 6.5	0 (0)	0 (0)	ELISA	**IL-21 ↑, TNF-α ↑**
113	Lokhande 2019	India	Own/modified	P	50 (60)	50 (50)	46.2, 14.9	35.1, 5.6	0 (0)	0 (0)	ELISA	**IL-21 ↑**
114	Loo 2012	China	AAP 1999	CP	440 (41)	850 (36)	49.3, 13.6	42.9, 9.7	NS	NS	ELISA	> 4 analytes ♦
115	Lönn 2014	Sweden	Own/modified	P	30 (57)	30 (57)	54.5, 31-74[b]	55.2, 27-74[b]	12 (40)	0 (0)	ELISA	**HGF ↑**
116	Mahendra 2022	India	AAP/EFP 2017	P	30 (80)	30 (77)	54.0, 9.1	37.6, 10.3	0 (0)	0 (0)	ELISA	**TNF-α ↑**
117	Manosudprasit 2017	USA	AAP 1999	CP	15 (40)	21 (48)	47.0, 9.0	38, 11	NS	NS	m-ELISA	sFasL TNF-α
118	Martinez-Herrera 2018	Spain	CDC/AAP 2007	CP	145 (66)	37 (57)	44.3, 10.7	40.0, 11.4	38 (26)	6 (16)	BBIA	**TNF-α ↑**
119	Martinez-Herrera 2018	Spain	Own/modified	CP	48 (56)	64 (81)	39.4, 8.3	36.8, 11.7	12 (25)	10 (16)	BBIA	**TNF-α ↑**, IL-6
120	Masi 2011	UK	Own/modified	P	356 (54)	207 (57)	46.9, 8.2	46.8, 10.2	121 (34)	87 (42)	ELISA	IL-6
121	Matić-Petrović 2016	Serbia	AAP 1999	CP	27 (59)	24 (71)	44.9, 12.5	42.0, 3.7	9 (33)	2 (8)	ELISA	TNFR2
122	McFarlane 1991	UK	Own/modified	P	26 (58)	20 (60)	29.1, 16-53[b]	29.1, 20-52[b]	NS	NS	ELISA	**IL-2 ↑, IL-2R ↑, IL-4 ↑**
123	Meraci 2020	Turkey	AAP/EFP 2017	Stage II-IIIB	40 (50)	20 (55)	41.9, 8.0	27.9, 6.2	4 (10)	5 (25)	ELISA	**ErbB4 ↑□**, Nrg4
124	Miranda 2019	Brazil	AAP 1999	CP	53 (66)	25 (68)	51.9, 8.0	51.6, 7.2	27 (51)	0 (0)	BBIA	> 4 analytes ♦
125	Miyazawa 2012	Japan	Own/modified	P	40 (68)	30 (47)	52.1, 11.9	46.1, 6.3	7 (18)	0 (0)	ELISA	IL-6, **PCSK9 ↑, TNF-α ↓**
126	Mohammad 2020	Iraq	Own/modified	P	60 (63)	30 (57)	36.7, 6.2	37.3, 7.1	0 (0)	0 (0)	ELISA	**IL-1β ↑, TNF-α ↑**
127	Mohan 2021	India	AAP/EFP 2017	Stage II-III	32 (44)	32 (50)	44.2, 7.1	33.8, 6.5	0 (0)	0 (0)	ELISA	**Procalcitonin ↑**
128	Mohit 2024	India	AAP/EFP 2017	Stage IIIB	11 (NS)	11 (NS)	35-65[a]	35-65[a]	0 (0)	0 (0)	ELISA	**Omentin ↓**
129	Mohite 2024	India	AAP/EFP 2017	Stage IIB	30 (NS)	30 (NS)	47.2	41.3	0 (0)	0 (0)	ELISA	**NT-proBNP ↑**
130	Nair 2016	India	AAP 1999	CP, AP	40 (NS)	20 (NS)	39.1, 4.9	26.3, 4.0	0 (0)	0 (0)	ELISA	**IL-18 ↑**
131	Nair 2022	India	AAP/EFP 2017	Stage II-III	30 (50)	30 (50)	36.5, 4.6	35.1, 4.2	0 (0)	0 (0)	ELISA	**Fetuin-A ↓**
132	Napimoga 2014	Brazil	AAP 1999	CP	15 (67)	15 (60)	46.5, 7.3	43.2, 6.2	0 (0)	0 (0)	ELISA	DKK1 **Sclerostin**

												↑, TNF-α ↑
133	Nethravathy 2014	India	AAP 1999	P	23 (NS)	22 (NS)	NS	NS	0 (0)	0 (0)	ELISA	HSP 60
134	Nizam 2014	Turkey	AAP 1999	GCP, GAgP	41 (51)	18 (39)	NS	44.5, 39.5-52.5	18 (44)	6 (33)	ELISA + IFA	MMP-8, **MPO ↑**, TIMP-1, NE
135	Noack 2017	Germany	Own/modified	P	20 (40)	19 (84)	50.3, 39.1-57.6[c]	24.3, 23.6-26.4[c]	4 (20)	0 (0)	ELISA	aMMP-8
136	Oner 2024	Turkey	AAP/EFP 2017	Stage I-IV	44 (41)	22 (36)	NS	32, 7	0 (0)	0 (0)	ELISA	**MIP-1a ↓□, MIF ↑□**
137	Ortiz-García 2019	Mexico	AAP 1999	CP	30 (50)	30 (50)	42.6, 9.1	39.2, 7.2	0 (0)	0 (0)	ELISA	MIF
138	Ozçaka 2011	Turkey	AAP 1999	CP	55 (36)	66 (48)	46.7, 8.8	40.7, 8.3	16 (29)	17 (26)	ELISA + IFMA	> 4 analytes ♦
139	Ozdemir 2019	Turkey	AAP 1999	P	30 (60)	20 (80)	49.9, 9.8	38.5, 8.6	0 (0)	0 (0)	ELISA	B-ALP, IGF-1
140	Padial-Molina 2015	USA	Own/modified	P	11 (36)	11 (27)	51, 29-71[c]	39, 22-70[c]	0 (0)	0 (0)	ELISA	Periostin
141	Pai 2021	India	Own/modified	P	30 (NS)	30 (NS)	30-60[a]	30-60[a]	0 (0)	0 (0)	ELISA	**IL-6 ↑**
142	Parihar 2024	India	Own/modified	P	36 (NS)	36 (NS)	25 - 55[a]	25 - 55[a]	0 (0)	0 (0)	ALP kit	**ALP ↑**
143	Peruma l 2014	India	AAP 1999	GCP	40 (NS)	40 (NS)	35-60[a]	35-60[a]	0 (0)	0 (0)	ELISA	**P-selectin ↑**
144	Pradeep 2009	India	Own/modified	CP	20 (NS)	20 (NS)	35.2, 2.9	32.3, 3.3	0 (0)	0 (0)	ELISA	**MCP-1 ↑**
145	Pradeep 2016	India	Own/modified	CP	17 (53)	10 (60)	41.5, 4.4	40.4, 3.9	0 (0)	0 (0)	ELISA	**caspase-3 ↑**
146	Preshaw 2020	UK	AAP 1999	P	44 (NS)	16 (NS)	47.5, 8.0[e]	48.5, 11.5[e]	NS	NS	ELISA	> 4 analytes ♦
147	Priyanka 2013	India	AAP 1999	CP	15 (47)	10 (50)	32.1, 3.2	34.2, 3.4	0 (0)	0 (0)	ELISA	Progranulin
148	Purwar 2015	India	Own/modified	CP	44 (50)	40 (68)	49.3, 8.1	49.9, 7.3	0 (0)	0 (0)	ELISA	**Leptin ↑**
149	Purwar 2015	India	AAP 1999	CP	22 (55)	22 (36)	35-60[a]	35-60[a]	0 (0)	0 (0)	ELISA	**Leptin ↑**
150	Rabelo 2021	Brazil	Own/modified	P	15 (60)	15 (33)	50.4, 8.1	45.3, 7.9	0 (0)	0 (0)	BBIA	> 4 analytes ♦
151	Raghavendra 2012	India	Own/modified	CP	15 (NS)	15 (NS)	38.8, 5.6	31.3, 3.5	0 (0)	0 (0)	ELISA	**Visfatin ↑**
152	Rahate 2022	India	AAP/EFP 2017	Stage III	60 (32)	30 (60)	52.1, 7.2	NS	30 (50)	0 (0)	ELISA	Ghrelin
153	Raj 2018	India	AAP 1999	CP	20 (50)	20 (50)	45.1, 7.7	40.1, 7.9	NS	NS	ELISA	IL-35
154	Raunio 2009	Finland	AAP 1999	CP	56 (66)	28 (64)	43.2, 9.2	40.0, 10.7	36 (64)	10 (36)	ELISA	**sCD14**
155	Ravindran 2023	India	AAP 1999	CP	8 (NS)	8 (NS)	35-55[a]	35-55[a]	0 (0)	0 (0)	ELISA	**Caspase-3 ↓, MFG-E8 ↓**
156	Rigi Ladez 2012	Iran	Own/modified	AgP, CP	61 (48)	35 (49)	31.5, 9.9	27.6, 8.7	0 (0)	0 (0)	ELISA	IL-8, IL-33, **IL-12 ↑**
157	Rughwani 2022	India	NS	NS	19 (42)	19 (47)	NS	NS	0 (0)	0 (0)	ELISA	**IL-6 ↑, PCSK9 ↑**
158	Sai 2020	India	AAP/EFP 2017	P	10 (NS)	10 (NS)	42.4, 6.8	22.2, 3.5	0 (0)	0 (0)	ELISA	**sCD163 ↑**
159	Sánchez-Hernández 2011	Mexico	AAP 1999	CP, AgP	30 (80)	9 (67)	42.2, 11.3	38.1, 14.6	0 (0)	0 (0)	ELISA	**IL-12 ↑□, IL-18 ↑**
160	Sasikumar 2022	India	Own/modified	CP	28 (NS)	28 (NS)	NS	NS	0 (0)	NS	ELISA	**IL-17A ↑**

161	Satpathy 2015	India	AAP 1999	P	10 (NS)	10 (NS)	25-49[a]	25-49[a]	0 (0)	0 (0)	ELISA	**IL-1β ↑**
162	Schenkein 2007	USA	AAP 1999	GAgP, CP	190 (58)	90 (56)	38.1, 11.5	35.2, 11.0	NS	NS	ELISA	sICAM, sE Selectin ↑□, sVCAM
163	Schenkein 2010	USA	AAP 1999	GAgP, LAgP	102 (68)	67 (57)	24.4, 5.7	22.9, 0.9	NS	NS	ELISA	**IL-17 ↑**
164	Scherbaum 2020	Germany	AAP 1999	P	146 (68)	60 (67)	47, 16.1[e]	28, 11.7[e]	NS	NS	ELISA	**proBNP ↑, IL-6 ↑, Tp1 ↑**
165	Şengül 2022	Turkey	AAP/EFP 2017	Stage IIIB	21 (57)	24 (67)	40.1, 2.2	34.6, 2.1	0 (0)	0 (0)	ELISA	IL-6
166	Sharma 2012	India	Own/modified	CP	10 (NS)	10 (NS)	32.6, 7.5	28.7, 3.6	0 (0)	0 (0)	ELISA	**CSTC ↑**
167	Shimada 2010	Japan	AAP 1999	CP	33 (76)	18 (72)	55.1, 7.8	52.2, 17.5	11 (33)	0 (0)	ELISA	**Leptin ↑,** Adiponectin, TNF-α, **IL-6 ↑**
168	Silosi 2015	Romania	Own/modified	CP	14 (57)	21 (67)	39-68[a]	35-58[a]	NS	NS	ELISA	**MMP-9 ↑**
169	Singh 2024	India	AAP 1999	CP	30 (50)	30 (50)	47.1	43.9	NS	NS	ELISA	**HBD-2 ↓**
170	Sllamniku-Dalipi 2013	Kosovo	Own/modified	P	75 (60)	35 (51)	45.1, 10.7	30.4, 5.7	44 (59)	15 (43)	ELISA	**IL-1β ↑, TNF-α ↑, IL-6 ↑**
171	Sophia 2020	India	AAP 1999	CP	30 (NS)	30 (NS)	NS	NS	0 (0)	0 (0)	ELISA	Resistin
172	Suresh 2022	India	AAP 1999	GCP	40 (NS)	40 (NS)	37.2, 4.8	36.8, 3.6	NS	NS	ELISA	**Resistin ↑**
173	Tan 2020	Turkey	AAP/EFP 2017	Stage I/III	40 (58)	20 (35)	40.5, 10.1	29.0, 5.6	0 (0)	0 (0)	ELISA	**IL-1β ↑, NGAL ↑,** IL-10
174	Tayman 2019	Turkey	AAP 1999	GAgP, CP	41 (59)	20 (60)	40.0 8.8	38.1, 8.1	0 (0)	0 (0)	ELISA	ADAMTS-1, HIF-1a, VEGF
175	Temelli 2018	Turkey	AAP 1999	CP	21 (33)	16 (63)	50, 42-71[c]	49, 33-65[c]	5 (24)	0 (0)	ELISA	> 4 analytes
176	Thilagar 2018	India	AAP 1999	CP	20 (90)	20 (65)	44.3, 14.0	36.2, 7.6	NS	NS	ELISA	**TNF-α ↑**
177	Thorat 2010	India	Own/modified	CP	20 (NS)	20 (NS)	30.6, 6.2	28.8, 3.8	0 (0)	0 (0)	ELISA	**Oncostatin M ↑**
178	Toker 2018	Turkey	AAP 1999	CP	51 (67)	50 (66)	33.4, 6.0	33, 6.5	0 (0)	0 (0)	ELISA	**IL-6 ↑, IL-10 ↑**
179	Tsuneto 2019	Brazil	AAP 1999	CP	18 (NS)	6 (NS)	NS	NS	0 (0)	0 (0)	ELISA	**IL-18 ↑,** MMP-9, IL12b
180	Turkmen 2023	Turkey	AAP/EFP 2017	Stage IIIB	20 (45)	20 (55)	41.1, 6.4	34.2, 7.4	0 (0)	0 (0)	ELISA	**IL-6 ↑,** Irisin
181	Turkoglu 2017	Turkey	AAP 1999	GAgP	26 (62)	25 (64)	31, 5	33, 6	0 (0)	0 (0)	ELISA	hCAP18/LL-37
182	Türer 2016	Turkey	AAP 1999	CP	15 (47)	15 (53)	38.7, 4.3	34.8, 4.5	0 (0)	0 (0)	ELISA	**Visfatin ↑**
183	Türer 2017	Turkey	AAP 1999	CP	20 (NS)	20 (NS)	NS	NS	0 (0)	0 (0)	ELISA	Endocan, **VEGF-A** ↑, TNF-a
184	Türer 2017	Turkey	AAP 1999	CP	20 (45)	20 (55)	36.3, 2.6	34.1, 3.3	0 (0)	0 (0)	ELISA	**Fetuin-A ↓, TNF-α ↑**
185	Wang 2020	China	AAP 1999	GAgP	216 (39)	138 (38)	27.3, 4.3	27.1, 4.2	0 (0)	0 (0)	ELISA	**EGF ↑**
186	Wang 2023	China	Own/modified	CP	36 (56)	25 (44)	44.8, 11.3	41.6, 9.7	0 (0)	0 (0)	ELISA	**Chemerin ↑, TNF-α ↑, IL-1 β ↑, IL-6 ↑**
187	Wick 2013	Switzerland	Own/modified	P	130 (44)	46 (46)	49.3, 44.6-58.5d	47.3, 42.9-58.4d	57 (44)	7 (15)	BBIA	**MMP-2 ↓, MMP-3, MMP-8 ↑, MMP-9↑**

188	Wohlfeil 2012	Germany	Own/modified	CP, AgP	60 (47)	30 (53)	42.3, 12.8	27.5, 3.3	19 (32)	8 (27)	ELISA	**IL-6 ↑□, Elastase ↑□**, IL-8
189	Wänman 2024	Sweden	AAP/EFP 2017	Stage III-IV	478 (59)	509 (57)	59, 49.0-66.0[e]	44.0, 39.0-50.0[e]	124 (26)	15 (3)	PEA	> 4 analytes ♦
190	Xu 2016	China	AAP 1999	CP	35 (54)	35 (51)	51.1, 7.9	48.9, 9.8	0 (0)	0 (0)	ELISA	OPG, **RANKL ↑**
191	Xu 2023	China	AAP 1999	CP	40 (55)	20 (60)	52.2, 9.7	33.6, 7.0	5 (13)	0 (0)	ELISA	**IL-17 ↑, Visfatin ↑**
192	Yemenoglu 2024	Turkey	AAP/EFP 2017	Stage III-IV	30 (50)	30 (47)	53.6, 5.9	52.4, 6.5	0 (0)	0 (0)	ELISA	> 4 analytes ♦
193	Yetkin Ay 2013	Turkey	AAP 1999	AgP	6 (67)	6 (50)	38.7, 3.5	32.3, 4.1	0 (0)	0 (0)	m-ELISA	> 4 analytes ♦
194	Yilmaz 2021	Turkey	AAP/EFP 2017	Stage III-IV	21 (48)	22 (59)	54, 35-63[c]	48, 34-66[c]	0 (0)	0 (0)	BBIA	**Fractalkine ↑,** MIF, MCP-1
195	Yilmaz 2024	Turkey	AAP/EFP 2017	Stage III-IV	24 (50)	24 (58)	52, 35-63[c]	49, 34-66[c]	0 (0)	0 (0)	ELISA	> 4 analytes ♦
196	Yilmaz 2024	Turkey	AAP/EFP 2017	Stage III	38 (53)	40 (48)	40.7, 9.6	38.5, 7.0	18 (47)	20 (50)	ELISA	IL-6
197	Yılmaz 2014	Turkey	AAP 1999	CP	35 (31)	35 (34)	36.9, 2.8	35.5, 3.7	0 (0)	0 (0)	ELISA	> 4 analytes ♦
198	Yılmaz Şaştım 2021	Turkey	CDC/AAP 2007	P	40 (35)	38 (58)	NS	NS	20 (50)	18 (47)	BBIA	> 4 analytes ♦
199	Zhang 2017	China	AAP 1999	CP, GAgP	22 (NS)	9 (NS)	NS	NS	0 (0)	0 (0)	ELISA	**CCL-2 ↑**
200	Zhang 2021	China	AAP 1999	CP	200 (NS)	200 (NS)	20-50[a]	20-50[a]	0 (0)	0 (0)	ELISA	IL-1b
201	Zhang 2024	China	AAP/EFP 2017	CP	156 (NS)	128 (NS)	45.3, 12.2	45.0, 12.7	42 (27)	31 (24)	ELISA	> 4 analytes ♦
202	Zia 2022	India	AAP/EFP 2017	CP	40 (100)	20 (100)	24.9, 2.2	20.1, 1.5	0 (0)	0 (0)	ELISA	CTX, ALP
203	Zimmermann 2013	Brazil	AAP 1999	CP	20 (75)	20 (70)	47.8, 7.7	42.9, 7.2	0 (0)	0 (0)	ELISA	> 4 analytes ♦
204	Önder 2023	Turkey	AAP/EFP 2017	Stage IIIB-C	46 (41)	48 (56)	NS	NS	22 (48)	24 (50)	LC-MS	IL-6
205	Öztürk 2021	Turkey	AAP/EFP 2017	Stage II-IV	42 (67)	59 (63)	42.7, 10.6	27.6, 7.8	5 (12)	8 (14)	ELISA	**hBD-2 ↓**
206	Öztürk 2015	Turkey	AAP 1999	CP, GAgP	41 (59)	20 (30)	39.3, 8.5	36.0, 11.8	NS	NS	ELISA	L-plastin

Abbreviations: AAP: American Academy of Periodontology; AgP: aggressive periodontitis; BBIA: bead-based immunoassay; CDC: Centers for Disease Control and Prevention; CP: chronic periodontitis; HPLC: high performance liquid chromatography; EL: electroluminescence; ECL: electrochemiluminescence immunoassay; EFP: European Federation of Periodontology; ELISA: enzyme-linked immunosorbent assay; EOP: early onset periodontitis; GAgP: generalized aggressive periodontitis; GCP: generalized chronic periodontitis; IFA: immunofluorometric assay; IFMA: time-resolved immunofluorometric assay; LAgP: localized aggressive periodontitis; LC-MS: liquid chromatography mass spectrometry; m-ELISA: multiplex enzyme-linked immunosorbent assay; NS: not specified; PEA: proximity extension assay; RIA: radioimmunoassay; SMSIA: sandwich multispot immunoassay.

* Subgroups of cases and controls were pooled. Mean age and standard deviation were calculated for the pooled group where sufficient data were available; a: range; b: mean and range; c: median and range; d:mean and 95% confidence interval; e: median and interquartile range; ± Significantly altered proteins between cases and controls are bolded with arrow indicating direction; □ Significantly altered in one subgroup of cases only, compared to controls; ♦ See original publication for proteins that were significantly altered between cases and controls

List of included studies with full study information (1-206) are provided in Supplementary material.

List of included proteins, with full name and abbreviation, are provided in Supplementary material, Supplementary table 6

In total, data from 17953 participants (9310 cases and 8643 controls) were included. Demographic data were reported by most of the included studies. Overall, males and females were represented relatively equally across studies. While 78 studies included smokers, the majority (n=128) focused on non-smoking participants. The most-reported method for quantifying protein concentration was enzyme-linked immunosorbent assay (ELISA) (*n* = 182, 88.3%). The second-most frequently used method was bead-based immunoassays (BBIA) (*n* = 14, 6.8%). The included studies were carried out in 28 different countries, with India contributing the most, at 55 studies (26.7%), followed by Turkey (25.7%) and China (7.8%). Most studies investigated just one or a few proteins (86.9%), and only a small number (13.1%) presented results for more than four proteins. Detailed demographic information for each study is presented in Table 1.

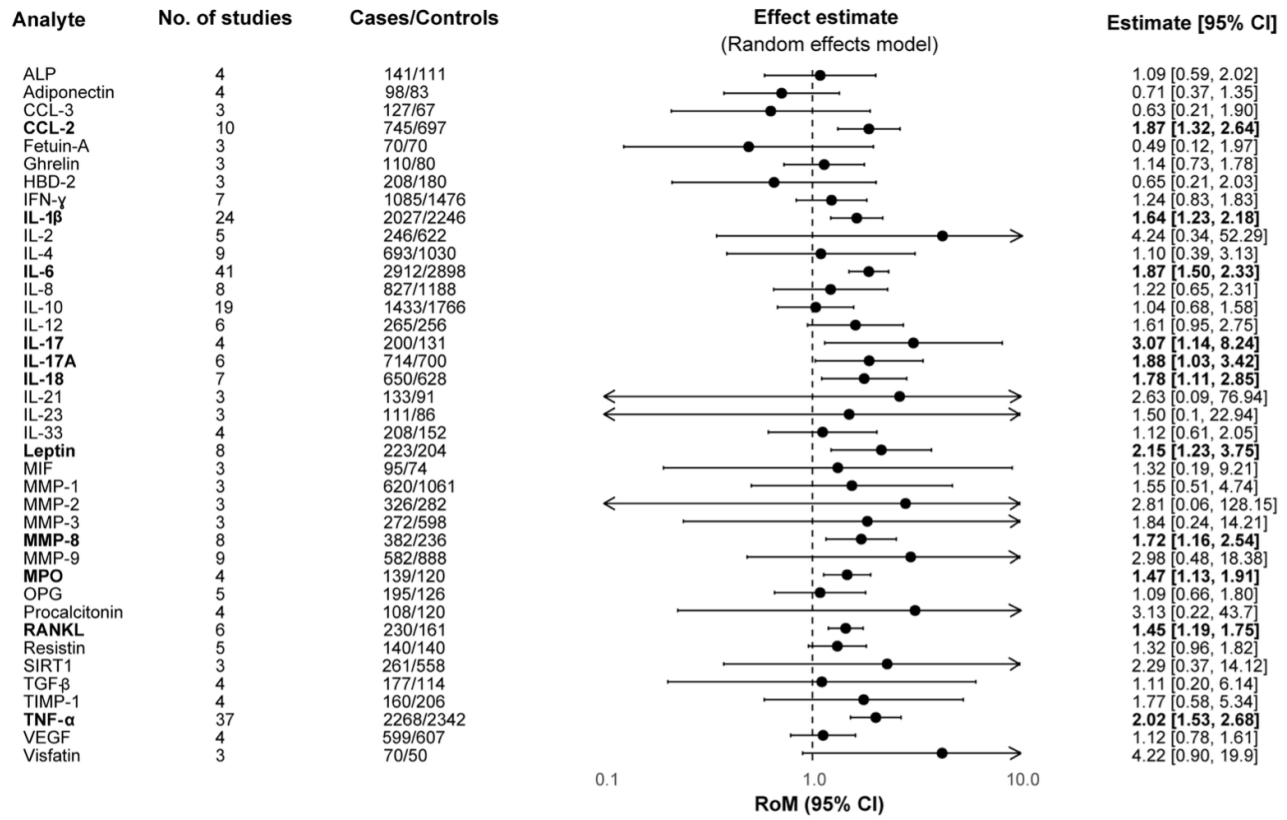

Figure 2. Meta-analysis of inflammatory proteins with a random-effects model. Forest plot depicting the ratios of means (RoM) with 95% confidence intervals (CI) for serum levels of the included proteins in periodontitis cases vs. healthy controls. RoM > 1 indicates higher levels of the protein in cases compared with controls; RoM < 1 indicates lower levels in cases. Significant alterations are bolded. ALP: alkaline phosphatase; CCL: C–C motif chemokine ligand; HBD-2: β-defensin 2; IFN-γ: interferon-gamma; IL: interleukin; MIF: macrophage migration inhibitory factor; MMP: matrix metalloproteinase; MPO: myeloperoxidase; OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor kappa-B ligand; SIRT1: sirtuin 1; TGF-β: transforming growth factor beta; TIMP-1: tissue inhibitor of metalloproteinases-1; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.

Among the included studies, 131 (63.6%) were rated as good quality, and 73 (35.5%) were rated as satisfactory quality. Two studies did not meet the criteria for the selection, comparability, and outcome domains in the quality assessment and were rated as unsatisfactory quality. No study was rated as very good quality because none received maximum scores in the selection and comparability domains, as no study applied a random sampling procedure or established comparability between non-respondents and respondents. In general, most studies scored well for the selection and outcome assessment but had limited comparability between groups, since the result was not adjusted for all relevant confounders (Supplementary Table 5).

Serum concentrations of 157 unique proteins were reported across the studies (Supplementary Table 6). The most frequently studied proteins in the included studies were IL-6 (47 studies), tumour necrosis factor (TNF)-α (41 studies), IL-1β (32 studies), and IL-10 (24 studies). A meta-analysis of 39 different proteins analysed in at least three studies (Table 2 and Fig. 2) demonstrated that the concentrations of 11 proteins—chemokine (C-C motif) ligand 2 (CCL2), IL-1β, IL-6, IL-17, IL-17A, IL-18, leptin, matrix metalloproteinase 8 (MMP-8), myeloperoxidase (MPO), receptor activator of nuclear factor kappa- B ligand (RANKL), and TNF-α—were elevated in the periodontitis group compared with the controls. Among the proteins included in the meta-analysis, IL-6 had the greatest number of studies available for pooling, with 41 studies including 2912 periodontitis cases and 2898 controls. TNF-α was included in 37 studies, comparing levels between 2268 cases and 2342 controls. IL-1β was included in 24 studies, comparing levels between 2027 cases and 2246 controls. The RoM and 95% CI for IL-6, TNF-α, and IL-1β were 1.87 (1.50–2.33), 2.02 (1.53–2.68), and 1.64 (1.23–2.18), respectively.

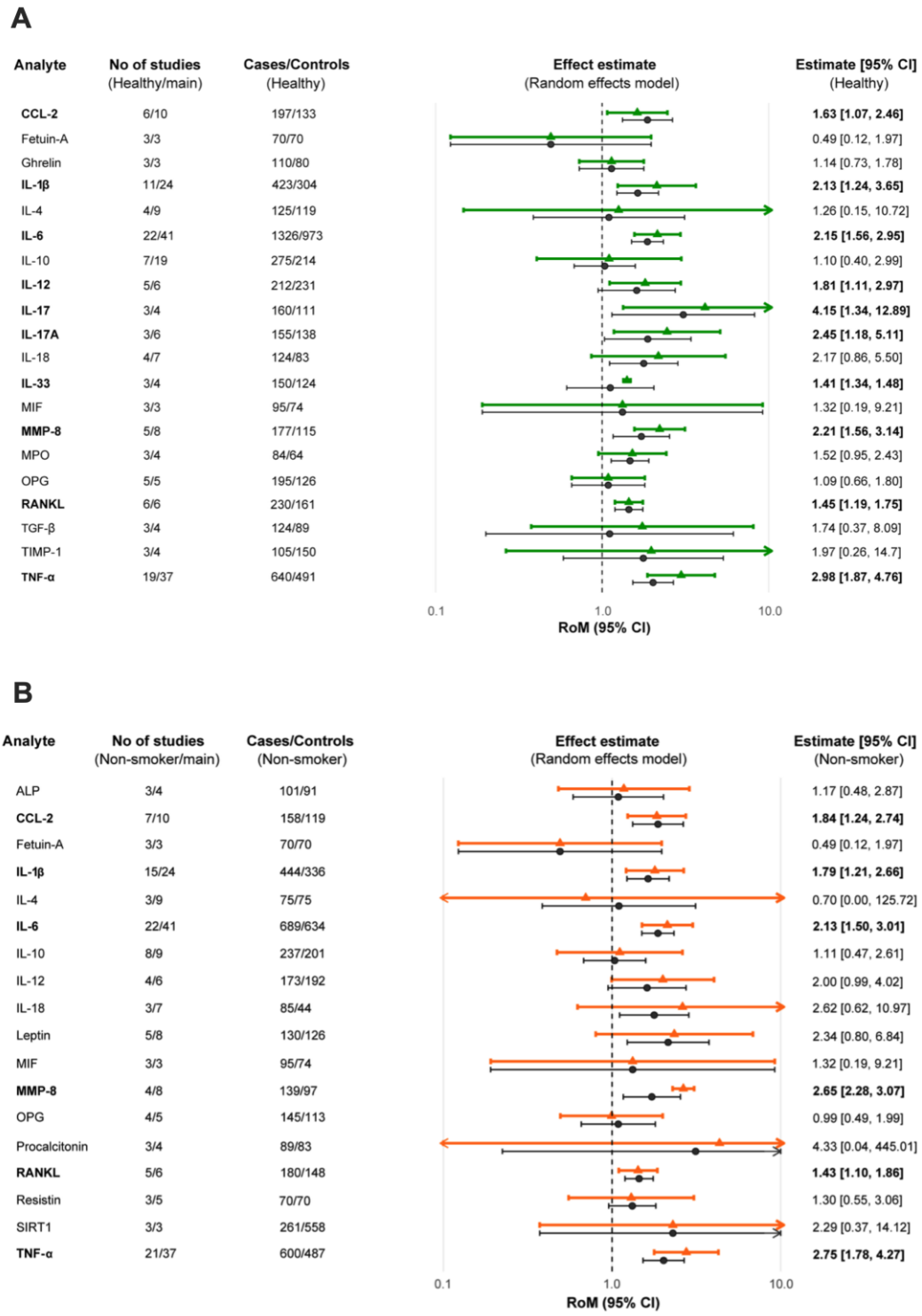

Figure 3. Meta-analysis of inflammatory proteins with a random-effects model in a subgroup restricted to systemically healthy (A) and non-smoking (B) participants. Forest plot depicting the ratios of means (RoM) with 95% confidence intervals (CI) for serum levels of the included proteins in systemically healthy participants (green colour), non-smoking participants (orange colour) and the main analysis (black colour). RoM > 1 indicates higher levels of the protein in cases compared with controls; RoM < 1 indicates lower levels in cases. Significant alterations are bolded. ALP: alkaline phosphatase; CCL: C–C motif chemokine ligand; IL: interleukin; MIF: macrophage migration inhibitory factor; MMP: matrix metalloproteinase; MPO: myeloperoxidase; OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor kappa-B ligand; SIRT1: sirtuin 1; TGF-β: transforming growth factor beta; TIMP-1: tissue inhibitor of metalloproteinases-1; TNF-α: tumor necrosis factor alpha.

A subgroup meta-analysis including only systemically healthy cases and controls was performed for 20 proteins, in which serum concentrations of 10 proteins (CCL2, IL-1β, IL-6, IL-12, IL-17, IL-17A, IL-33, MMP-8, RANKL, and TNF-α) were significantly elevated in periodontitis cases compared with controls (Table 2 and Fig. 3A). A second subgroup meta-analysis including only non-smokers was performed for 18 proteins and showed significantly elevated levels of CCL2, IL-1β, IL-6, MMP-8, RANKL, and TNF-α among non-smoking periodontitis cases (Table 2 and Fig. 3B). Significantly altered levels of CCL2, IL-1β, IL-6, MMP-8, RANKL, and TNF-α were demonstrated in both main and subgroups analysis.

The heterogeneity between studies for each protein was generally high, ranging from 0.46 to 1.0 in both the main and subgroup analyses, except for IL-33 in systemically healthy participants (I^2 = 0.00) and MMP-8 in non-smokers (I^2 = 0.00). The τ^2 varied considerably across proteins, with larger between-study variance observed for IL-6, TNF-α, and IL-1β. This resulted in wide prediction intervals for all included proteins, except for IL-33 and MMP-8, in their respective subgroup analysis. Egger's regression test for publication bias indicated significant bias for IL-6 (intercept = -4.98, p-value = 0.03) and IL-10 (intercept = -6.22, p-value =0.03) in the main analysis. However, both analyses were characterized by substantial between-study heterogeneity, which may influence funnel plot symmetry. No significant bias was detected for IL-1β (intercept = 1.65, p-value = 0.77), TNF-α (intercept = 0.37, p-value = 0.88) or CCL2 (intercept = -4.67, p-value = 0.66. No significant bias was detected for any of the three proteins in the subgroup analyses that were eligible for Egger's test (i.e., IL-1β, IL-6, and TNF-α). Exclusion of influential studies did not materially alter the direction or statistical significance of the association. The pooled RoM decreased from 1.87 to 1.74 (95% CI 1.45–2.10) for IL-6, from 2.02 to 1.90 (95% CI 1.47–2.46) for TNF-α, and from 1.64 to 1.50 (95% CI 1.18–1.89) for IL-1β.

Table 2. Random-effects meta-analysis of protein levels as RoM in periodontitis cases and controls, including subgroup analysis.

Protein	Group	Studies	Studies in MA	Case (*n*)	Control (*n*)	RoM (95% CI)	*P* value	I^2	τ^2	Prediction interval
Adiponectin	Main analysis	6	4	98	83	0.71 (0.37–1.35)	0.188	0.73	0.11	0.21–2.40
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
ALP	Main analysis	4	4	141	111	1.09 (0.59–2.02)	0.690	0.97	0.13	0.30–3.97
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	3	3	101	91	1.17 (0.48–2.87)	0.519	0.98	0.12	0.20–6.86
CCL-2	Main analysis	12	10	745	697	1.87 (1.32–2.64)	**0.003**	1.00	0.23	0.60–5.84
	Healthy only	8	6	197	133	1.63 (1.07–2.46)	**0.030**	0.98	0.15	0.55–4.83
	Non-smoking	8	7	158	119	1.84 (1.24–2.74)	**0.009**	0.97	0.18	0.61–5.55
CCL-3	Main analysis	6	3	127	67	0.63 (0.21..1.90)	0.212	0.56	0.00	0.30–1.31
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
Fetuin-A	Main analysis	3	3	70	70	0.49 (0.12–1.97)	0.159	0.99	0.31	0.03–7.79
	Healthy only	3	3	70	70	0.49 (0.12–1.97)	0.159	0.99	0.31	0.03–7.79
	Non-smoking	3	3	70	70	0.49 (0.12–1.97)	0.159	0.99	0.31	0.03–7.79
Ghrelin	Main analysis	3	3	110	80	1.14 (0.73–1.78)	0.339	0.46	0.02	0.49–2.63
	Healthy only	3	3	110	80	1.14 (0.73–1.78)	0.339	0.46	0.02	0.49–2.63
	Non-smoking	..	..	..	..	..	..	..	..	..
HBD-2	Main analysis	3	3	208	180	0.65 (0.21–2.03)	0.246	0.92	0.19	0.07–5.68
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
IFN-ɣ	Main analysis	10	7	1085	1476	1.24 (0.83–1.83)	0.235	0.97	0.17	0.41–3.69
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-1β	Main analysis	32	24	2027	2246	1.64 (1.23–2.18)	**0.002**	1.00	0.45	0.40–6.74
	Healthy only	14	11	423	304	2.13 (1.24–3.65)	**0.011**	0.99	0.63	0.34–13.48
	Non-smoking	17	15	444	336	1.79 (1.21–2.66)	**0.007**	0.99	0.49	0.38–8.47
IL-2	Main analysis	8	5	246	622	4.24 (0.34..52.29)	0.185	0.99	4.05	0.01–1943.15
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-4	Main analysis	13	9	693	1030	1.10 (0.39–3.13)	0.842	1.00	1.50	0.05–22.32

	Healthy only	6	4	125	119	1.26 (0.15–10.72)	0.758	1.00	1.81	0.01–150.91
	Non-smoking	5	3	75	75	0.70 (0.00–125.72)	0.794	1.00	3.50	0.00–10020.51
IL-6	Main analysis	47	41	2912	2898	1.87 (1.50–2.33)	**<0.001**	0.99	0.41	0.51–6.92
	Healthy only	24	22	1326	973	2.15 (1.56–2.95)	**<0.001**	1.00	0.48	0.49–9.41
	Non-smoking	23	22	689	634	2.13 (1.50–3.01)	**<0.001**	0.99	0.52	0.45–9.95
IL-8	Main analysis	10	8	827	1188	1.22 (0.65–2.31)	0.477	0.98	0.47	0.21–7.08
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-10	Main analysis	24	19	1433	1766	1.04 (0.68–1.58)	0.864	0.99	0.67	0.18–6.08
	Healthy only	10	7	275	214	1.10 (0.40–2.99)	0.823	0.99	1.14	0.07–18.14
	Non-smoking	10	8	237	201	1.11 (0.47–2.61)	0.781	0.99	1.03	0.09–14.14
IL-12	Main analysis	9	6	265	256	1.61 (0.95–2.75)	0.069	0.98	0.19	0.47–5.53
	Healthy only	7	5	212	231	1.81 (1.11–2.97)	**0.029**	0.98	0.11	0.66–5.00
	Non-smoking	5	4	173	192	2.00 (0.99–4.02)	0.051	0.97	0.13	0.52–7.64
IL-17	Main analysis	6	4	200	131	3.07 (1.14–8.24)	**0.036**	0.97	0.37	0.34–27.71
	Healthy only	4	3	160	111	4.15 (1.34–12.89)	**0.033**	0.85	0.16	0.52–33.06
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-17A	Main analysis	8	6	714	700	1.88 (1.03–3.42)	**0.043**	0.96	0.31	0.40–8.89
	Healthy only	4	3	155	138	2.45 (1.18–5.11)	**0.034**	0.83	0.07	0.63–9.55
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-18	Main analysis	8	7	650	628	1.78 (1.11–2.85)	**0.024**	0.97	0.24	0.49–6.43
	Healthy only	4	4	124	89	2.17 (0.86–5.50)	0.076	0.98	0.32	0.28–16.79
	Non-smoking	3	3	85	44	2.62 (0.62–10.97)	0.102	0.98	0.32	0.15–46.11
IL-21	Main analysis	3	3	133	91	2.63 (0.09–76.94)	0.342	0.95	1.32	0.00–1904.97
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-23	Main analysis	3	3	111	86	1.50 (0.10–22.94)	0.586	0.96	1.15	0.01–318.28
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
IL-33	Main analysis	7	4	208	152	1.12 (0.61–2.05)	0.595	0.98	0.15	0.27–4.56
	Healthy only	3	3	150	124	1.41 (1.34–1.48)	**0.001**	0.00	0.00	1.25–1.59
	Non-smoking	..	..	..	..	..	..	..	..	..
Leptin	Main analysis	11	8	223	204	2.15 (1.23–3.75)	**0.014**	0.98	0.33	0.50–9.20
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	6	5	130	126	2.34 (0.80–6.84)	0.093	0.99	0.62	0.21–25.72
MIF	Main analysis	3	3	95	74	1.32 (0.19–9.21)	0.597	0.82	0.47	0.04–43.07
	Healthy only	3	3	95	74	1.32 (0.19–9.21)	0.597	0.82	0.47	0.04–43.07
	Non-smoking	3	3	95	74	1.32 (0.19–9.21)	0.597	0.82	0.47	0.04–43.07
MMP-1	Main analysis	3	3	620	1061	1.55 (0.51–4.74)	0.234	0.99	0.19	0.17–14.08
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
MMP-2	Main analysis	3	3	326	282	2.81 (0.06–128.15)	0.364	1.00	2.36	0.00–5804.31
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
MMP-3	Main analysis	3	3	272	598	1.84 (0.24–14.21)	0.329	0.99	0.67	0.03–109.43
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
MMP-8	Main analysis	8	8	382	236	1.72 (1.16–2.54)	**0.013**	0.97	0.20	0.56–5.32
	Healthy only	5	5	177	115	2.21 (1.56–3.14)	**0.003**	0.59	0.05	1.04–4.70
	Non-smoking	4	4	139	97	2.65 (2.28–3.07)	**<0.001**	0.00	0.00	2.00–4.3.50
MMP-9	Main analysis	10	9	582	888	2.98 (0.48–18.38)	0.204	1.00	5.59	0.01–932.76
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..
MPO	Main analysis	4	4	139	120	1.47 (1.13–1.91)	**0.018**	0.52	0.01	0.94–2.30
	Healthy only	3	3	84	64	1.52 (0.95–2.43)	0.062	0.52	0.02	0.76–3.05
	Non-smoking	..	..	..	..	..	..	..	..	..
OPG	Main analysis	5	5	195	126	1.09 (0.66–1.80)	0.668	0.87	0.10	0.41–2.90
	Healthy only	5	5	195	126	1.09 (0.66–1.80)	0.668	0.87	0.10	0.41–2.90
	Non-smoking	4	4	145	113	0.99 (0.49–1.99)	0.986	0.86	0.08	0.36–2.76
Procalcitonin	Main analysis	5	4	108	120	3.13 (0.22–43.70)	0.263	1.00	2.73	0.01–1128.20
	Healthy only	..	..	..	..	..	..	..	..	..

	Non-smoking	4	3	89	83	4.33 (0.04–445.01)	0.306	1.00	3.46	0.00–45127.23
RANKL	Main analysis	6	6	230	161	1.45 (1.19–1.75)	**0.004**	0.65	0.01	1.02–2.05
	Healthy only	6	6	230	161	1.45 (1.19–1.75)	**0.004**	0.65	0.01	1.02–2.05
	Non-smoking	5	5	180	148	1.43 (1.10–1.86)	**0.020**	0.74	0.02	0.94–2.16
Resistin	Main analysis	5	5	140	140	1.32 (0.96–1.82)	0.076	0.93	0.06	0.62–2.80
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	3	3	70	70	1.30 (0.55–3.06)	0.319	0.89	0.11	0.24–6.95
SIRT1	Main analysis	3	3	261	558	2.29 (0.37–14.12)	0.188	0.79	0.42	0.08..63.53
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	3	3	261	558	2.29 (0.37–14.12)	0.188	0.79	0.42	0.08..63.53
TGF-β	Main analysis	5	4	177	114	1.11 (0.20–6.14)	0.860	0.99	1.08	0.03–45.53
	Healthy only	4	3	124	89	1.74 (0.37–8.09)	0.260	0.99	0.38	0.08–37.20
	Non-smoking	..	..	..	..	..	..	..	..	..
TIMP-1	Main analysis	4	4	160	206	1.77 (0.58–5.34)	0.200	0.99	0.48	0.15–20.79
	Healthy only	3	3	105	150	1.97 (0.26–14.70)	0.283	0.99	0.65	0.04–108.57
	Non-smoking	..	..	..	..	..	..	..	..	..
TNF-α	Main analysis	41	37	2268	2342	2.02 (1.53–2.68)	**<0.001**	0.99	0.62	0.40–10.24
	Healthy only	21	19	640	491	2.98 (1.87–4.76)	**<0.001**	0.99	0.78	0.44–19.99
	Non-smoking	22	21	600	487	2.75 (1.78–4.27)	**<0.001**	0.99	0.78	0.42–18.13
VEGF	Main analysis	5	4	599	607	1.12 (0.78–1.61)	0.375	0.53	0.03	0.59–2.14
	Healthy only	..	..	..	..	..	**..**	..	..	..
	Non-smoking	..	..	..	..	..	**..**	..	..	..
Visfatin	Main analysis	3	3	70	50	4.22 (0.90–19.90)	0.057	0.99	0.38	0.19–92.12
	Healthy only	..	..	..	..	..	..	..	..	..
	Non-smoking	..	..	..	..	..	..	..	..	..

RoM: ratio of means; CI: confidence interval; MA: Meta-analysis. Heterogeneity across studies was assessed using I^2 and τ^2.

DISCUSSION

Periodontitis is the sixth most common non-communicable disease globally and has systemic effects extending beyond the oral cavity. Driven by chronic cytokine-mediated inflammation, it contributes to local tissue breakdown and subsequent widespread immune activation. This systematic review and meta-analysis provide insight into the systemic inflammatory and immunological disturbances that accompany periodontitis. Circulating levels of CCL2, IL-1β, IL-6, IL-17, IL-17A, IL-18, leptin, MMP-8, MPO, RANKL, and TNF-α were significantly increased in individuals with periodontitis compared with healthy controls. This validates and extends findings from previous narrative reviews [9, 10] and smaller studies [12-14]. Importantly, associations for CCL2, IL-1β, IL-6, IL-17, IL-17A, MMP-8, RANKL, and TNF-α and additional significant associations for IL-12 and IL-33 were demonstrated in the subgroup analyses restricted to systemically healthy participants. Moreover, significant associations for CCL2, IL-1β, IL-6, MMP-8, RANKL, and TNF-α were detected in non-smoking periodontitis cases. Collectively, beyond the purely statistical estimates and albeit limitations in stratifications, the findings indicate that the systemic inflammatory changes are driven by biological responses related to periodontitis itself rather than by comorbid conditions, including systemic diseases and smoking.

The inflammatory profile characterised by elevated IL-6, TNF-α, and IL-1β levels in periodontitis overlaps with that observed in metabolic syndrome, type 2 diabetes, and CVD, supporting the concept that periodontal inflammation may contribute to systemic low-grade inflammation and metabolic dysregulation [23-25]. This is further supported by increased leptin and MPO, which are implicated in insulin resistance and endothelial dysfunction [26, 27]. Such shared inflammatory signatures may help explain the association between periodontitis and metabolic disorders.

Periodontal inflammation evolves from early macrophage- and neutrophil-dominated lesions to established lymphocyte-rich infiltrates. However, skewed proportions and differential activities of certain lymphocyte subsets have been described in periodontitis and are proposed to sustain chronic inflammation and tissue degradation in recurrent disease [28]. For example, elevated IL-17 and IL-18 in this study may reflect local dominance of T helper 17 (Th17) cells and Th17/regulatory T cells (Treg) imbalance – a mechanism implicated in both periodontitis and related autoimmune diseases such as RA [29].

Beyond adaptive immunity, maladaptive trained innate immunity may also contribute to the disease pathogenesis of various diseases, including periodontitis, by inducing a persistent pro-inflammatory 'memory' in innate immune cells. Epigenetic reprogramming enables these cells to respond rapidly to repeated microbial stimulation, sustaining a long-lasting destructive pro-inflammatory phenotype [8]. Cytokines such as IL-1β, IL-6, and particularly IL-17 play central roles in

maintaining this maladaptive immune memory by amplifying myeloid cell activation and sustaining inflammatory cytokine loops [30]. The elevated systemic levels of IL-1β, IL-17, and IL-6 observed in this study link periodontitis to systemic inflammatory priming, chronic inflammatory comorbidities and periodontitis flares.

The concept of inflammaging links unfavourable serum cytokine profiles with unhealthy ageing and frailty. Experimental periodontitis increases systemic TNF-α and IL-1β levels and is associated with multi-organ frailty, including cognitive decline in mice [31]. The elevated levels of TNF-α, IL-1β, IL-6, IL-18, IL-17, and CCL2 observed in this meta-analysis suggest that periodontitis could accelerate inflammatory ageing and bone resorption [1]. Reduced bone mineral density and osteoporosis, increasingly prevalent in frail older adults, result from increased bone resorption and/or impaired bone formation and are associated with periodontitis [32]. The chemokine CCL2 recruits osteoclasts and amplifies RANKL-induced osteoclastogenesis, and the elevated levels of both CCL2 and RANKL in periodontitis and osteoporosis [33, 34], suggest that persistent periodontal inflammation may exacerbate bone loss in metabolic bone disorders.

The validity of the findings in this review is supported by several key strengths. First, the comprehensive search incorporated a large number of studies across diverse populations, thereby substantiating the robustness and increasing the generalisability of the results. The increases in specific proteins remained significant when the analysis was restricted to systemically healthy participants and non-smokers, which underscores the strength of the evidence by minimising potential confounding factors. However, it must be considered that only a proportion of the proteins included in the main analysis were eligible for inclusions in the subgroup analysis, rendering fewer significant associations.

Nonetheless, important limitations should be acknowledged. Substantial heterogeneity was observed across studies, possibly reflecting both methodological and biological sources of variation. Differences in case definition and periodontal classification systems, including varying diagnostic thresholds and definitions of disease severity, may influence both case identification and how the underlying inflammatory burden is expressed systemically. This, in turn, could potentially affect the pooled estimates and contribute to between-study heterogeneity. In addition, other methodological sources of variation are likely present. This includes differences in population demographics, sampling procedures, and protein quantification methods (e.g., detection limits, sensitivity, and specificity), potentially adding to the variability of the outcomes. For example, the geographic clustering of studies and noting that the predominance of studies from certain regions (e.g., India and Turkey) may influence the generalizability of the findings due to differences in population characteristics, environmental exposures, and healthcare contexts. Given the substantial heterogeneity observed across studies, the pooled RoM should be interpreted with caution. These estimates likely reflect an average across heterogeneous study contexts and mainly indicate the overall direction and consistency of association between biomarkers and disease. The magnitude of the pooled estimates may vary across populations and study settings, which may limit their generalizability. In addition, the RoM represents the relative difference in biomarker levels between individuals with periodontitis and controls, allowing comparison across studies using different measurement scales, and should therefore be interpreted as a relative difference rather than an absolute clinical threshold. As the meta-analyses relies primarily on cross-sectional data, elevated systemic cytokine levels may reflect bidirectional relationships between periodontal inflammation and systemic inflammatory status, rather than a strictly causal pathway.

Although subgroup analyses restricted to non-smokers or systemically healthy participants were performed to partially address heterogeneity, the pooled estimates were largely derived from unadjusted aggregate study-level data, with most studies reporting only overall results from cases and controls. Therefore, residual confounding cannot be excluded. Factors such as age, sex, metabolic status, medication use, and disease stage represent biologic sources of variation which may influence systemic cytokine levels and thus contribute to the observed associations. The limited availability of stratified or adjusted estimates in the primary studies further restricts assessment of potential effect modification. Furthermore, most studies assessed only a limited number of biomarkers within hypothesis-driven frameworks, leading to the repeated investigation of well-known mediators such as IL-6 and TNF-α, while other potentially relevant proteins remained understudied. Egger's test indicated potential small-study effect for IL-6 and IL-10, which could reflect publication bias. However, given the substantial heterogeneity, funnel plot asymmetry cannot be attributed solely to publication bias. Taken together, future studies should focus on harmonized data collection following internationally adopted criteria for periodontitis classification [17], together with sufficient granularity of data to allow meaningful stratification.

From a public health perspective, these results strengthen the evidence that effective prevention and management of periodontitis could play a role in reducing systemic inflammation and mitigating the risk of inflammatory comorbidities and unhealthy aging. Policymakers should recognise periodontal care as a

scalable cost-effective component of public health strategies targeting healthy ageing and should be integrate periodontal assessment into general health strategies. Future research should use standardised case definitions, multiplex proteomics, and well-characterised longitudinal cohorts to clarify causal links and determine whether periodontal interventions can modulate systemic cytokine profiles, influence disease trajectories, and support integrative approaches to oral and systemic health.

Contributors

EK, MW, AL, and PL contributed to the conceptualisation and design of the study; EK, MW and KHM acquired data; MW and WW analysed data; EK, MW, WW, AL, and PL interpreted data; and EK, MW, and PL drafted the manuscript. All authors critically reviewed the manuscript, approved the final version of the manuscript, and are accountable for all aspects of the work. EK and MW contributed equally and share first authorship. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

We declare no competing interests.

Supplementary Materials

The Supplementary data are available online at: www.aginganddisease.org/EN/10.14336/AD.2026.0110.

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