



Serum IL-17, IL-34, and CXCL12 in Plaque-Induced Gingivitis: An Exploratory Case-Control Study

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Abstract

Background: Plaque-induced gingivitis is a common inflammatory periodontal condition in which alterations in inflammatory and immune mediators such as IL-17, IL-34, and CXCL12 may reflect the host response to dental plaque. **Objective:** This study assessed whether plaque-induced gingivitis was accompanied by altered serum concentrations of three types of interleukin IL-17, IL-34, and CXCL12 and, in a small ancillary subset, whether these markers varied with the dominant cultured isolate. **Methodology:** This exploratory case-control study enrolled 30 adults: 15 with plaque-induced gingivitis and 15 periodontally healthy controls. Serum IL-17, IL-34, and CXCL12 were measured by enzyme-linked immunosorbent assay. Between-group comparisons were based on two-sided Mann-Whitney U tests with Holm adjustment for the three prespecified biomarkers, and Welch unequal-variance t tests were used as sensitivity analyses. In eight gingivitis cases, dominant aerobic isolates were recovered by culture and the corresponding cytokine distributions were summarized descriptively. **Results:** Compared with controls, gingivitis cases showed higher serum IL-17 (median 83.62 vs 65.07 pg/mL; Holm-adjusted $p = 0.0084$) and a markedly higher serum IL-34 concentration (766.17 vs 64.98 pg/mL; Holm-adjusted $p = 1.02 \times 10^{-5}$). Serum CXCL12 remained similar in the two groups ($p = 0.8682$). Within the ancillary bacterial subset, cytokine values differed numerically across isolates, but the subgroup sizes were too small to support organism-level inference. **Conclusion:** In this exploratory cohort, plaque-induced gingivitis was accompanied by higher circulating IL-17 and, more strikingly, IL-34. Among the three analytes, IL-34 yielded the clearest separation between groups and deserves validation in larger serum-based studies of early gingival inflammation. The ancillary bacterial findings were descriptive and should not be read as evidence for isolate-specific effects. [Bangladesh Journal of Infectious Diseases, June 2026;13(1):300-307]

Keywords: Plaque-induced gingivitis; serum biomarkers; interleukin-17; interleukin-34; CXCL12; case-control study

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Introduction

Plaque-induced gingivitis is the most prevalent reversible periodontal lesion, which is an inflammatory response to dental plaque contained in the gingival tissues. In the present classification of periodontal disease, the diagnosis is made on

clinical symptoms of periodontal inflammation such as bleeding on probing without attachment loss due to periodontitis. Although it has been suggested that gingivitis is reversible, this should not be interpreted to mean that they have limited biological relevance, as gingivitis is frequently the first

clinically apparent sign of a host reaction to plaque accumulation, and when inflammation continues, may be one of the stages in the progression of periodontal breakdown¹⁻⁴.

This has turned from using only descriptive clinical indices to a more detailed molecular evaluation of the early gingival lesion. Gingivitis has been shown to be linked to changes in immune mediators and tissue-remodeling signals in the gingival crevicular fluid, saliva, and gingival tissue before clinical signs of irreversible tissue destruction is evident^{5,6}. The systemic inflammatory changes observed in plaque-induced gingivitis, particularly IL-17 and IL-34, are consistent with findings from previous studies on oxidative stress and inflammatory biomarkers^{7,8}. Such local changes, however, do not necessarily reflect serum changes. A serum-based investigation thus investigates a different question: Are there measurable systemic changes that accompany clinically localized inflammation of the gingiva^{9,10}. IL-17 is a biologically plausible candidate since it correlates with microbial challenge, Th17 activity, neutrophil recruitment and amplification of inflammatory cascades. IL 17 has been observed to be elevated throughout the spectrum of health to gingivitis to periodontitis in human periodontal fluid (HGF) and IL 17 producing T cells have been identified within long-standing gingivitis lesions. The recent systematic review of the IL 23/IL 17 axis reaffirms the idea that signaling of the IL 17 pathway is already dysregulated in gingivitis and not just in late periodontitis¹¹⁻¹³.

There are fewer studies on IL 34 in gingival disease, but recent findings indicate that it may play important roles in regulating myeloid cells and remodeling tissues. Human gingival fibroblasts can express IL-34, and pro-inflammatory cytokines like TNF- α and IL-1 β increase its expression; IL-34 can also facilitate differentiation of osteoclasts, suggesting a mechanism for inflammatory tissue turnover. In periodontal disease, clinical studies have been performed on gingival tissue, gingival crevicular fluid, and plasma in which IL-34 was detected, but more limited data have been obtained in serum in plaque-induced gingivitis¹⁴⁻¹⁶. A related, but distinct chemokine pathway is the activation of CXCL12 (stromal cell-derived factor-1 α), which is also involved in leukocyte migration, stromal cell communication, angiogenesis, and recruitment of progenitor cells. The CXCL12/CXCR4 axis has been detected in periodontal tissue cells such as gingival fibroblasts and gingival tissues, and higher levels of CXCL12 have been found in periodontal lesions, while there

is evidence that the axis is modulatory during the inflammatory process induced by *Porphyromonas gingivalis*. However, serum data are still scarce, particularly for the early and reversible gingivitis¹⁷⁻¹⁹.

The evidence available suggests that the biological relevance of assessing IL-17, IL-34, and CXCL12 in gingival inflammation is supported; however, it offers little in the way of information regarding the behavior of these mediators in the circulation during plaque-induced gingivitis. Based on this, we compared plaque-induced gingivitis patients with periodontally healthy controls in terms of serum levels of these cytokines, which are IL-17, IL-34, and CXCL12. In a small secondary subset, we also investigated whether the levels of serum cytokines were different depending on the dominant cultured isolate from gingivitis sites. We predicted that the levels of circulating IL-17 and IL-34 would be higher in participants with gingivitis, and that the systemic expression of CXCL12 would be more variable.

Methodology

Study Settings and Population: This study aimed to conduct a single-center exploratory case-control study of serum IL-17. The levels of IL-34 and CXCL12 were not different between patients with plaque-induced gingivitis and periodontally healthy controls. It was carried out at the Dental Teaching Hospital, Tikrit and Tikrit University, and was performed from January 2024 to May 2025, Salah al-Din, Iraq. Blood sampling and clinical assessment taken at Dental Teaching Hospital, with the laboratory analyses conducted throughout the Dental Teaching Hospital Central Laboratories, the laboratories of the College of Science, and the Postgraduate Studies Laboratories. The analytical sample consisted of 30 adults, 15 with plaque induced A total of 15 periodontally healthy controls and 121 gingivitis (cases) were included in the serum biomarker profile data. Since this was an exploratory study and a hypothesis-generating study, no formal a priori sample size calculation was done; it was a convenience sample that was enrolled to provide effect-size estimates. The goal of this one was to provide information for planning power calculations for future confirmatory studies. Culture-based bacterial an ancillary subset of the gingivitis group (n = 8).

Participant Recruitment and Periodontal Case Definition: Participants were recruited from the Dental Teaching Hospital. Assignment to study groups was based on the contemporary

classification framework for plaque-induced gingival conditions²⁻⁴. Gingivitis was diagnosed when plaque-associated gingival inflammation was present, with bleeding on probing affecting more than 20.0% of the examined sites, probing depths not exceeding 3 mm, and no clinical attachment loss or radiographic bone loss compatible with periodontitis. The absence of clinical attachment loss (CAL), probing depths of 3 mm or less, and the absence of no calculus were defined as health. Bleeding on probing that is below the level that would be considered gingivitis. Adults aged 25 to 55, Only those 18 or older were eligible to be included. Anyone who was a smoker, pregnant or breastfeeding was excluded. Lactating, had diabetes mellitus, systemic inflammatory or autoimmune disease, had received recent had not received periodontal treatment, or had received systemic antibiotics or anti-inflammatory drugs within the past three months. Predefined washout period

Blood Collection and Serum Preparation:

Peripheral venous blood (5 mL) was collected under aseptic conditions into serum separator tubes (SST) without anticoagulant. Samples were allowed to clot for 30 min at room temperature and were then centrifuged at 1500 to 2000 × g for 10 to 15 min to separate serum. The serum fraction was aliquoted into sterile microtubes and stored at -80°C until analysis. Repeated freeze-thaw cycles were avoided (no more than 1 to 2 cycles).

Measurement of serum IL-17, IL-34, and CXCL12: Serum IL-17, IL-34, and CXCL12 were measured with commercial sandwich enzyme-linked immunosorbent assay kits (Sunlong Biotech, Hangzhou, China), including Cat. No. EL0199Hu for IL-17, SL3267Hu for IL-34, and EL0249Hu for CXCL12, following the manufacturers' instructions. Standards and serum samples were assayed in duplicate, and concentrations were derived from plate-specific standard curves. Analytical sensitivity, measuring range, and intra- and inter-assay coefficients of variation followed the manufacturer's documentation. Case and control samples were processed in a single batch, and laboratory measurements were performed without knowledge of clinical grouping.

Microbiological sampling and bacterial identification: An ancillary culture-based microbiological dataset was available for eight gingivitis cases. Supragingival plaque or oral swab samples were collected from the most inflamed or index sites using sterile swabs. Samples were inoculated onto blood agar and incubated

aerobically at 37°C for 48 h. From each specimen, the predominant colony morphotype was selected as the dominant isolate and identified using the VITEK 2 automated system with Gram-positive identification cards (GP, version 08.01) (bioMérieux, Marcy l'Étoile, France). The ancillary subset comprised *Kocuria rosea* (n = 3), *Staphylococcus lentus* (n = 4), and *Leuconostoc pseudomesenteroides* (n = 1). Because this approach relied on aerobic culture and dominant-isolate selection, it was considered descriptive and hypothesis-generating rather than a comprehensive microbiome analysis.

Statistical Analysis: This study is reported in accordance with the STROBE guideline for observational studies and its molecular-epidemiology extension (STROBE- ME)^{20,21}. All 30 serum samples had complete measurements for IL-17, IL-34, and CXCL12; no imputation was therefore required. Analyses were performed in Python. Continuous variables are reported as median (interquartile range) in the primary analysis and as mean ± standard deviation in sensitivity analyses. Normality was assessed with the Shapiro-Wilk test. Because the biomarker distributions were not consistently normal, case-control comparisons were based on two-sided Mann-Whitney U tests. Holm's procedure was used to adjust p-values across the three prespecified biomarker comparisons. For each analyte, rank-biserial correlation and the Hodges-Lehmann estimate of the between-group shift with its 95.0% confidence interval were reported. Welch unequal-variance t-tests with Hedges' g were used as sensitivity analyses. Given the modest sample size, no multivariable adjustment, receiver operating characteristic analysis, or internal validation procedure was attempted. In the secondary microbiological subset, cytokine distributions across dominant isolates were summarized descriptively and explored with the Kruskal-Wallis test; because one isolate category contained a single observation, these analyses were treated as ancillary and were not used for organism-specific inference. All tests were two-sided, and adjusted p < 0.05 was considered statistically significant.

Ethical Consideration: The Research Ethics Committee of the College of Science, Tikrit approval this study. University of Salah al-Din, Iraq (SC1TUH-0007; 20 December 2024). All the procedures were carried out following the Declaration of Helsinki principles. Informed consent, in writing, was obtained from all

participants before enrollment.

Results

Thirty participants entered the final serum biomarker analysis: 15 with plaque-induced gingivitis and 15 periodontally healthy controls. Complete serum measurements were available for IL-17, IL-34, and CXCL12 in all 30 participants, so no case was excluded for missing laboratory data. Culture-based bacterial identification data were also available for a secondary subset of eight gingivitis cases, which formed the isolate-stratified analysis. At least one of the study arms was non-normal for each analyte, so the main case-control comparisons utilized two-sided Mann-Whitney U-tests. The concentration of serum IL-17 was increased in the gingivitis group compared with healthy controls. The median IL-17 concentration was 83.62 pg/mL (IQR, 78.40 to 100.21) in gingivitis and 65.07 pg/mL (IQR, 57.48 to 77.44) in controls. The difference between groups was 20.99 pg/mL (95.0% CI, 2.44 to 36.14), and was still significant after Holm adjustment (adjusted $p = 0.0084$).

A significant difference between the two groups was obtained with IL-34. Median serum IL-34 was 766.17 pg/mL (IQR, 742.49–889.49) in the gingivitis group and 64.98 pg/mL (IQR, 58.89–78.60) in healthy controls. The Hodges-Lehmann estimate of the between-group shift was 701.19 pg/mL (95% CI, 673.56–822.18), with a highly significant Holm-adjusted p value (1.02×10^{-5}).

In contrast, they found no difference in the serum CXCL12 between the two groups. The median CXCL12 concentration was 985.91 pg/mL (IQR, 953.47–1051.44) in gingivitis and 982.82 pg/mL (IQR, 950.90–1058.34) in controls. No significant difference was found between groups ($p = 0.8682$),

the Hodges-Lehmann estimate of the between-group shift was -3.95 pg/mL (95% CI, -85.83 to 55.38). The results are summarized below in Tables 1, and shown below in Figure 1.

Sensitivity analysis

The general non-parametric analysis and the mean based Welch sensitivity analysis were both pointing in the same direction. IL-17 and IL-34 were still elevated in gingivitis while CXCL12 was not significant. These secondary results supplement the stability of the primary results, but should be interpreted within the framework of a small exploratory data set. The full sensitivity analysis is shown in Supplementary Table S1.

There are significant associations between serum cytokine levels and other specific bacteria in the dominant isolated bacterial species of patients with gingivitis. Eight of 15 patients with gingivitis had culture-based data. *Staphylococcus lentus*, *Kocuria rosea* and *Leuconostoc pseudomesenteroides* were the predominant recovered isolates in 4, 3 and 1 cases, respectively. Serum cytokine levels were found to be numerically different between these isolate groups, but it was not possible to make reliable organism-specific interpretations as there were limited numbers of observations in each subgroup.

The patient with *Leuconostoc pseudomesenteroides* as the predominant isolate had the highest serum levels of IL-17 (183.40 pg/mL) and IL-34 (972.54 pg/mL) and the lowest level of CXCL12 (631.54 pg/mL). Patients with *S. lentus* as the main pathogen had the highest overall median CXCL12 level (1024.83 pg/mL) and interquartile range (991.35–1093.70 pg/mL). The median levels of serum IL-17, IL-34, and CXCL12 were 102.88 pg/mL, 766.32 pg/mL, and 947.17 pg/mL,

Table 1: Primary Non-Parametric Comparison of Serum Cytokines Between Gingivitis and Healthy Controls

Biomarker	Gingivitis median (IQR), pg/mL	Healthy controls median (IQR), pg/mL	Hodges-Lehmann shift estimate (95% CI), pg/mL	Mann-Whitney U	p value	Holm-adjusted p value	Rank-biserial correlation
IL-17	83.62 (78.40–100.21)	65.07 (57.48–77.44)	20.99 (2.44 to 36.14)	182	0.0042	0.0084	0.618
IL-34	766.17 (742.49–889.49)	64.98 (58.89–78.60)	701.19 (673.56 to 822.18)	225	3.38×10^{-6}	1.02×10^{-5}	1.000
CXCL12	985.91 (953.47–1051.44)	982.82 (950.90–1058.34)	-3.95 (-85.83 to 55.38)	108	0.8682	0.8682	-0.040

Footnote: Primary inference was based on two-sided Mann-Whitney U tests because at least one study arm showed non-normality for each biomarker. P values were adjusted using the Holm procedure.

respectively, for *Kocuria rosea*. No significant differences were found between the groups of isolates for serum levels of IL-17 (Kruskal-Wallis $p = 0.201$), IL-34 ($p = 0.200$), or CXCL12 ($p = 0.143$).

Due to the small subgroup size in this part of the analysis (particularly the *Leuconostoc* isolate), this result should be considered in a descriptive way, and not as evidence of the presence of the organism.

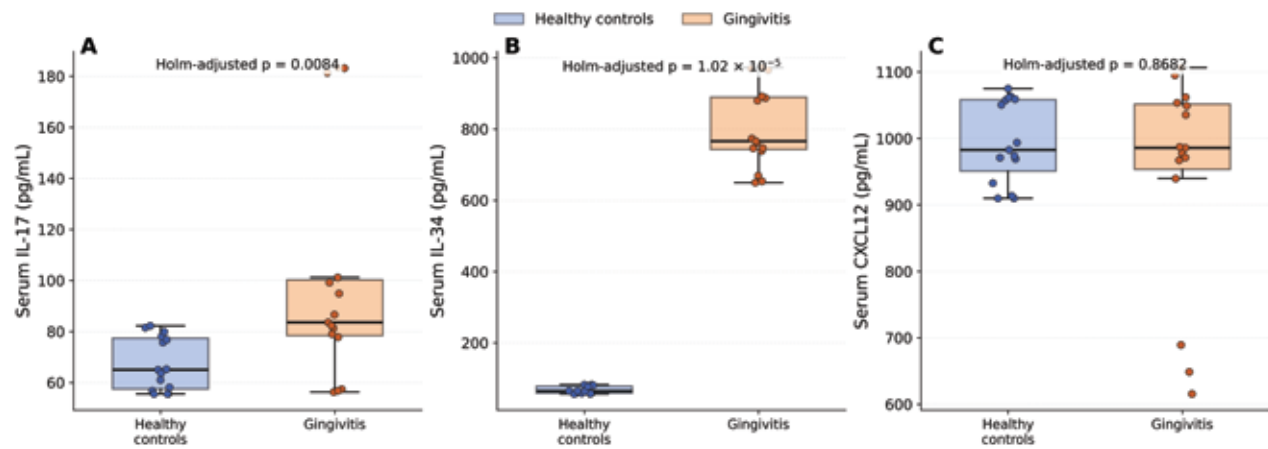


Figure 1: Box-and-whisker plots for serum concentrations of IL-17, IL-34 and CXCL12 in healthy controls and patients with plaque-induced gingivitis. Boxes represent interquartile range; median line; whiskers represent non-outlier values; and points represent individual participants. Primary Mann-Whitney U analysis p values are Holm adjusted.

Table 2: Ancillary exploratory serum cytokine concentrations according to dominant isolated bacterial species among gingivitis patients

Dominant isolated bacterium	n	IL-17 median (IQR), pg/mL	IL-34 median (IQR), pg/mL	CXCL12 median (IQR), pg/mL
<i>Kocuria rosea</i>	3	102.88 (92.64–131.07)	766.32 (756.77–897.01)	947.17 (928.56–983.51)
<i>Staphylococcus lentus</i>	4	83.33 (76.06–88.07)	650.48 (633.40–708.40)	1024.83 (991.35–1093.70)
<i>Leuconostoc pseudomesenteroides</i>	1	183.40	972.54	631.54
Kruskal-Wallis p value	—	0.201	0.200	0.143

Values are reported as median (interquartile range) because of the small subgroup sizes. The *Leuconostoc pseudomesenteroides* group included a single isolate; therefore, comparisons involving this organism are descriptive only and not suitable for organism-specific inference

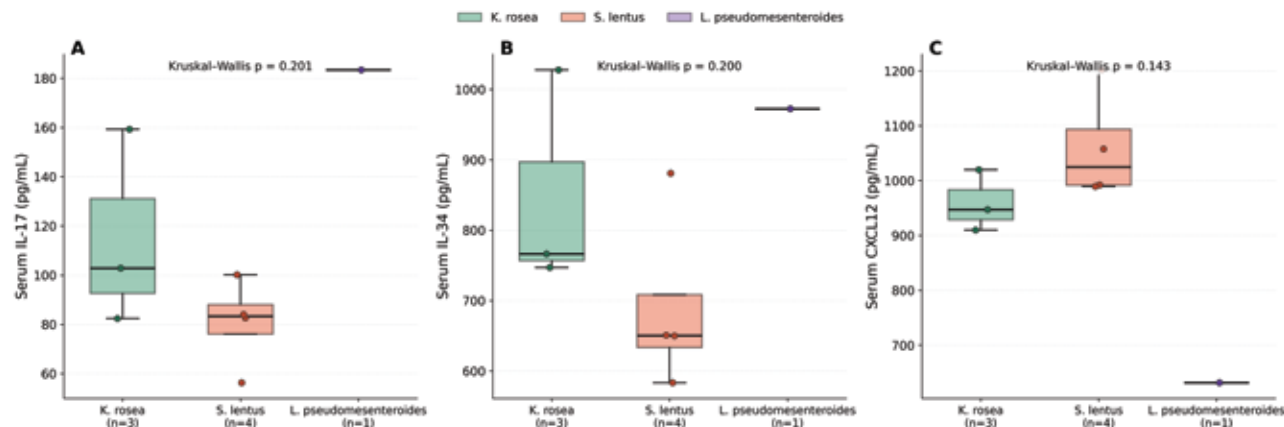


Figure 2: Means and SDs of serum IL-17, IL-34, and CXCL12 levels by dominant isolated bacterial species in the secondary gingivitis subset. Interquartile range is marked by boxes, median line by points representing individual participants. The Kruskal-Wallis test was used to determine the p-values for the panels. Data for the *Leuconostoc pseudomesenteroides* category is descriptive, as there was only one isolate in this category

Discussion

The main findings of this study were that adults with plaque-induced gingivitis had higher levels of both IL-17 and, more significantly, IL-34 in their blood, and there was little difference in the level of blood CXCL12 between the two groups. This discovery suggests that a lesion manifesting as a clinical problem involving only the gingival tissues may have systemic immune mediator(s) detectable. However, the results are to be interpreted with due caution because of the exploratory nature of this work, the rather small sample size, the recruitment from a single center, and the cross-sectional design.

IL-34 is especially notable in the present analysis, as it showed the clearest separation between gingivitis cases and healthy controls. This finding is consistent with the current biological view of this mediator. IL-34 is expressed by gingival fibroblasts; its production can be enhanced by pro-inflammatory cytokines, and it has been implicated in the regulation of myeloid cells as well as in pathways related to osteoclast activity^{14,15}. IL-34 has also been reported to influence macrophage responses to *Porphyromonas gingivalis*, linking it to periodontal host-microbe interactions²², and to the inflammatory bone loss that can accompany sustained periodontal inflammation²³. A similar increase in IL-34 has also been observed in clinical studies of gingival crevicular fluid and plasma from patients with periodontal disease¹⁶. In this context, our findings with serum imply that the Mechanisms mediated by IL-34 could be activated at a stage of which the attachment loss is not clinically observed. evident. The size of this difference, however, must be taken with some caution until similar results are confirmed in independent populations.

This pattern is also consistent with current theories of gingival immunobiology for IL-17. This cytokine is associated with inflammatory activity mediated by Th17, recruits neutrophils, and aids in enhancing the activation of cytokine signaling networks in the local area. Previous studies have shown an increase in IL-17 in gingival in addition to the presence of IL-17-producing T cells in gingivitis lesions¹¹⁻¹³, the crevicular fluid contained high levels of IL-17¹⁴⁻¹⁶.

The data presented here indicate that some of this inflammatory activity may be systemic, deteriorating the periodontal environment and would be measurable in serum, but systemic changes would be. They will likely be less apparent when measured directly in gingival tissues or crevicular fluid. In contrast, serum CXCL12 was not able to differentiate gingivitis from periodontally healthy controls. This result does not indicate that the CXCL12/CXCR4

axis is not involved in very few processes relevant to gingival inflammation. More likely it is that CXCL12 acts mainly in establishing local chemokine gradients instead of creating a stable output signal of circulating signals. This interpretation is in line with previous reports that have indicated CXCL12/CXCR4 expression in gingival fibroblasts and increased levels of CXCL12 in periodontal tissues. lesions¹⁷⁻¹⁹. In the present cohort, this lack of a clear serum difference is more reflective of that more activity in the compartment than of nothingness. The interpretation of the secondary microbiological findings must be made even more judiciously. Only eight patients with gingivitis were included in the analysis, with one isolate group represented by one. The bacterial assessment was performed by identifying the predominant aerobic culture, and the individual assessment was made using the indicator outlined in the individual assessment protocol. Instead of general microbiome characterization, isolate analysis. Because of this, there is an absolute difference in numbers. For *Kocuria rosea*, *Staphylococcus lentus*, and *Leuconostoc pseudomesenteroides*, there was an increase in observed frequency. Should be considered descriptive. It does not give evidence for any one cultured species.

The study does have some strengths; however, despite these drawbacks. The analysis was carried out on a well-balanced case-control serum dataset. Three biologically relevant inflammatory mediators within the case-control serum dataset were evaluated: Three serum markers that are biologically significant inflammatory mediators were assessed in the case-control serum dataset. The same cohort, employing a statistical method that included a correction for multiple testing, Estimation of effect sizes, and sensitivity analyses. Meanwhile, several restrictions ought to be acknowledged. The sample size was relatively small, and the cross-sectional design leaves out the possibility of temporal trends. Local periodontal compartments, rather than the single tooth being studied, were the unit of analysis. Inference and adjustment for potential covariates were not possible; Measurements of serum levels were not made along with GCF.

There were no other clear signals in this serum dataset, with IL-34 showing the strongest signal and IL-17 showing an additional. Evidence supporting the possibility of systemic inflammatory changes with plaque-induced gingivitis. More detailed studies with full clinical phenotyping and explicit assay quality control of both local and systemic samples. Documentation and culture-independent microbiome

profiling will be necessary to determine whether these results apply to other cohorts.

Conclusion

In this exploratory case-control study, plaque-induced gingivitis was accompanied by higher serum IL-17 and, more clearly, IL-34, whereas serum CXCL12 remained similar to the control range. Within the limits of this dataset, IL-34 showed the strongest between-group signal and is the analyte most worth testing in larger studies of early gingival inflammation.

Acknowledgements

None

Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this study.

Financial Disclosure

None

Authors' contributions

Lina Qays Yaseen conceived and designed the study, performed data collection and laboratory work, analyzed the data, interpreted the findings, and drafted the manuscript.

Data Availability

Any questions regarding the availability of the study's supporting data should be addressed to the corresponding author, who can provide it upon justifiable request.

Ethics Approval and Consent to Participate

Ethical approval was granted by the Research Ethics Committee of the College of Science, Tikrit University, Salah al-Din, Iraq (reference no. SC1TUH-0007; 20 December 2024). The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

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How to cite this article: Yaseen LQ. Serum IL-17, IL-34, and CXCL12 in Plaque-Induced Gingivitis: An Exploratory Case-Control Study *Bangladesh J Infect Dis* 2026;13(1): 300-307

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Article Info

Received on: 1 June 2025

Accepted on: 12 October 2025

Published on: 1 June 2026

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