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Original Article

Bacterial–host interactions in periodontal prognosis: Role of *P. gingivalis* and IL-8

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Abstract *Background/purpose:* The combined effects of *Porphromonas gingivalis* with other pathogens and host inflammatory on treatment prognosis remain underexplored. This study investigated associations between *P. gingivalis* bacterial co-infection, salivary IL-8 levels, and prognosis following non-surgical periodontal therapy (NSPT).
Materials and methods: Seventy-four participants underwent NSPT were recruited. Subgingival specimens were collected before treatment and analyzed by 16S rRNA sequencing. Salivary IL-8 levels and periodontal clinical parameters were recorded at baseline and one month after scaling and root-planing (SRP). Saliva samples were analyzed for IL-8 levels using a commercial kit. Multivariate regression analyses were conducted to assess associations between pathogens, IL-8, and prognosis.
Results: Participants with *Prevotella intermedia* had significantly higher IL-8 levels at baseline and post-treatment ($P = 0.03$ and $P < 0.01$). *P. gingivalis* was associated with significantly higher percentages of sites with PD $\geq$ 5 mm at both time points ($P = 0.04$ and $P = 0.02$). After adjusting for IL-8 and smoking, *P. gingivalis* was associated with higher residual PD $\geq$ 5 mm (5.11 %, $P < 0.05$), but lost significance after adjusting for oral health behaviors. After full adjustment, baseline *P. gingivalis* without *Aggregatibacter actinomycetemcomitans* was associated with higher residual PD $\geq$ 5 mm (7.83 %, $P < 0.05$), whereas co-infection attenuated this association (−0.49 %, $P > 0.05$).
Conclusion: P. gingivalis was associated with residual PD $\geq$ 5 mm, with its effect modified by

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smoking status, IL-8 levels, and oral health behaviors. Although co-infection with *A. actinomycetemcomitans* showed no significant effect, the attenuating trend warrants further investigation.

Introduction

Periodontitis is a multifactorial inflammatory disease, and the clinical response to standard non-surgical treatment varies significantly among individuals.[1] While conventional therapy can improve periodontal conditions in many patients, a subset of individuals continues to show poor treatment prognosis.[2] This variability highlights the lack of reliable prognostic biomarkers to guide personalized treatment planning.

Periodontitis is associated primarily with 'red complex' Gram-negative bacteria. Among these, *Porphyromonas. gingivalis* plays a particularly significant pathogenic role, expressing proteolytic enzymes such as gingipains, which degrade host tissue and immune barriers, induce apoptosis in gingival epithelial cells, and modulate both innate and adaptive immune responses.[3] These mechanisms contribute to establishing mature dental plaque biofilms and persistent inflammation.[4]

In addition to red complex bacteria, species like *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans* also contribute to periodontal pathogenesis.[5] *F. nucleatum* acts as a bridging organism, linking early and late colonizers in biofilm formation and promoting multispecies interactions through communication, metabolic cooperation, and cross-feeding.[6] It coadheres with *P. gingivalis*, facilitating biofilm maturation and disease progression.[7] *P. intermedia* can coaggregate with *P. gingivalis*, enhancing plaque formation and creating a synergistic pathogenic relationship that supports immune evasion.[8] *P. gingivalis* may outcompete *A. actinomycetemcomitans* in biofilm formation, influencing microbial composition and periodontitis severity.[9]

Periodontal pathogens such as *P. gingivalis*, along with host inflammatory responses (particularly the chemokine interleukin-8, IL-8), play critical roles in disease progression.[4] IL-8, a pro-inflammatory CXC chemokine, primarily attracts and activates neutrophils through various biochemical reactions and is implicated in various other cellular processes.[10]

Our previous study showed that high salivary IL-8 levels were significantly associated with the prognosis of non-surgical periodontal therapy,[11] while a recent study demonstrated that decreased salivary IL-8 levels correlated with effective periodontitis treatment.[12] However, most prior studies have examined pathogen presence and IL-8 levels separately, with limited investigation of their combined impact on treatment outcomes.

During calculus formation, *P. gingivalis*, *F. nucleatum*, *P. intermedia*, and *A. actinomycetemcomitans* play distinct roles at different stages.[5] Most previous studies have focused on the impact of individual bacterial species, whereas multi-species investigations are predominantly *in vitro*. Periodontal pathogens elicit host inflammatory responses, and periodontal disease arises from these complex microbial communities that trigger inflammation and lead to progressive tissue destruction.[13] Non-surgical periodontal therapy remains the standard treatment to suppress pathogenic microorganisms and restore a host-compatible microbiota, yet treatment responses vary considerably among patients due to individual risk factors.[14] Nevertheless, few studies on treatment outcomes have considered host inflammation and bacterial infection together, and the combined effects of *P. gingivalis* co-infection with other pathogens and host inflammatory status on treatment prognosis remain underexplored. This study aimed to investigate the associations between *P. gingivalis* and bacterial co-infection, salivary IL-8 levels, and prognosis following non-surgical periodontal therapy.

Materials and methods

This study was approved by the Ethics Committee of the Taipei Medical University Joint Institutional Review Board N201802045 (Taipei, Taiwan).

Participant recruitment

Participants were recruited from the Department of Dentistry at a medical university hospital and were eligible for the Comprehensive Periodontal Treatment Project (CTPT), a National Health Insurance program aimed at reducing periodontal disease in Taiwan.[15] Eligible participants met the following criteria: they were first-time visitors for periodontitis treatment, had more than 15 functional teeth, and presented probing depths (PD) of $\geq$5 mm in at least six teeth. Additionally, they had not previously received non-surgical periodontal therapy. Patients were excluded if they had a history of periodontal treatment, were pregnant, or had been diagnosed with cancer. Nighty-five patients participated in this study by convenience sampling. After excluding participants who did not complete treatment or whose samples were of insufficient quality for IL-8 detection and 16S rRNA sequencing, 74 cases were included in the final analysis.

Age, gender, tobacco use, and oral health behaviors are established risk factors for periodontal disease.[16] To account for these variables, a structured questionnaire was administered before treatment by a trained interviewer. Oral health behaviors (tooth brushing frequency and dental visits) were assessed by self-report. Tooth brushing

frequency was defined as the number of brushings per day. Dental visits were defined as attending a dental appointment within the past six months. Smoker was defined as current tobacco use.

Specimen collection and determination

The subgingival bacterial profile of subgingival samples was collected from participants' first scaling and root-planing (SRP). DNA was extracted using proteinase K digestion followed by phenol–chloroform extraction, and microbial communities were analyzed by 16S rRNA gene sequencing. Detailed procedures for specimen collection and sequencing have been described previously.[11] The presence of *P. gingivalis*, *F. nucleatum*, *P. intermedia*, and *A. actinomycetemcomitans* was confirmed s was confirmed when read counts greater than zero.

Baseline and post-treatment saliva were collected for IL-8 analysis. Prior to sample collection, participants rinsed with water to remove debris. Then they chewed wax for 5 min to stimulate saliva, which was collected using the Saliva-Check kit (GC Corporation, Tokyo, Japan). Samples were immediately placed on ice and transported to the laboratory. Each sample was mixed with a protease inhibitor cocktail (Roche Applied Science, Mannheim, Germany) at a ratio of 1 mL saliva to 10 μL inhibitor. The mixture was centrifuged at 3,000 rpm for 3 min and supernatants were stored at −20 °C until analysis.[17] IL-8 levels in the saliva were quantified using the MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel Kit (Merck Millipore, Darmstadt, Germany). The coefficient of variation for IL-8 measurements was 0.61 %.

Clinical parameters and treatment evaluation

Clinical examinations and non-surgical periodontal treatments, including subgingival scaling and root planing, and oral hygiene instruction, were performed. The procedures for measuring bleeding on probing (BOP), and probing depth (PD) - followed our previously described methodology.[18] BOP, and PD were expressed as percentages, calculated by dividing the number of positive sites by the total number of available sites. The mean periodontal probing depth (mean PD) was also calculated as an index of clinical condition.

According to a previous study, participants with >15 % of periodontal sites exhibiting probing depths (PD) > 5 mm had a 2.34-fold higher hazard of periodontal-related tooth loss.[19] In this study, participants were classified as poor prognosis to SRP if, one months after treatment, more than 15 % of sites had probing depths greater than 5 mm.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). As the data were not normally distributed, the non-parametric Mann–Whitney U test was used to assess differences in salivary IL-8 levels and clinical indicators based on the presence or absence of specific biotas. For comparisons involving different bacterial combinations, the Kruskal–Wallis test followed by Bonferroni post hoc test analysis was applied.

To further evaluate the associations between pathogens, IL-8, and treatment prognosis, univariate and multivariate regression analyses were conducted. Potential confounders, including smoking status, toothbrushing frequency, and dental visit regularity, were included as independent variables in the multivariate models. A *P*-value <0.05 was considered statistically significant.

Results

Table 1 presents the distribution of confounding factors such as age, sex, smoking status, and oral health behavior, and the detection of periodontal pathogens. Among the 74 participants (36 males, 38 females; mean age, 53.48 years), approximately 25.68 % of the participants were smokers; 43.2 % brushed more than twice daily; and 86.5 % had a dental visit within the past six months. Detection rates of *P. gingivalis*, *F. nucleatum*, *P. intermedia*, and *A. actinomycetemcomitans* were 24.32 %, 87.65 %, 93.24 % and 50.00 %, respectively.

Fig. 1 presents the distribution of baseline and one-month post-treatment IL-8 levels and periodontal clinical parameters according to bacterial presence. Participants with *P. intermedia* had significantly higher baseline IL-8 levels than those without infection (median 431.34 vs. 102.91 ng/mL; Fig. 1A, $P = 0.03$), and this difference

Table 1 Demographic characteristics, oral hygiene behavior, and presence of periodontal pathogens among study participants.

Demographic characteristics: *N* (%)	
Age (yrs), Mean ± SD	53.48 ± 10.97
Sex, *N* (%)	
Male	36 (48.65)
Female	38 (51.35)
Smoking status, *N* (%)	
Non-smoker	55 (74.32)
Smoker	19 (25.68)
Tooth brushing frequency	
1 or 2 times/day	42 (56.76)
> twice/day	32 (43.24)
Dental visit, *N* (%)	
<6 months	64 (86.49)
≥6 months	10 (13.51)
Periodontal pathogens, *N* (%)	
P. gingivalis	
Not detected	56 (75.68)
Present	18 (24.32)
F. nucleatum	
Not detected	9 (12.35)
Present	65 (87.65)
P. intermedia	
Not detected	5 (6.76)
Present	69 (93.24)
A. actinomycetemcomitans	
Not detected	37 (50.00)
Present	37 (50.00)

SD: standard deviation.

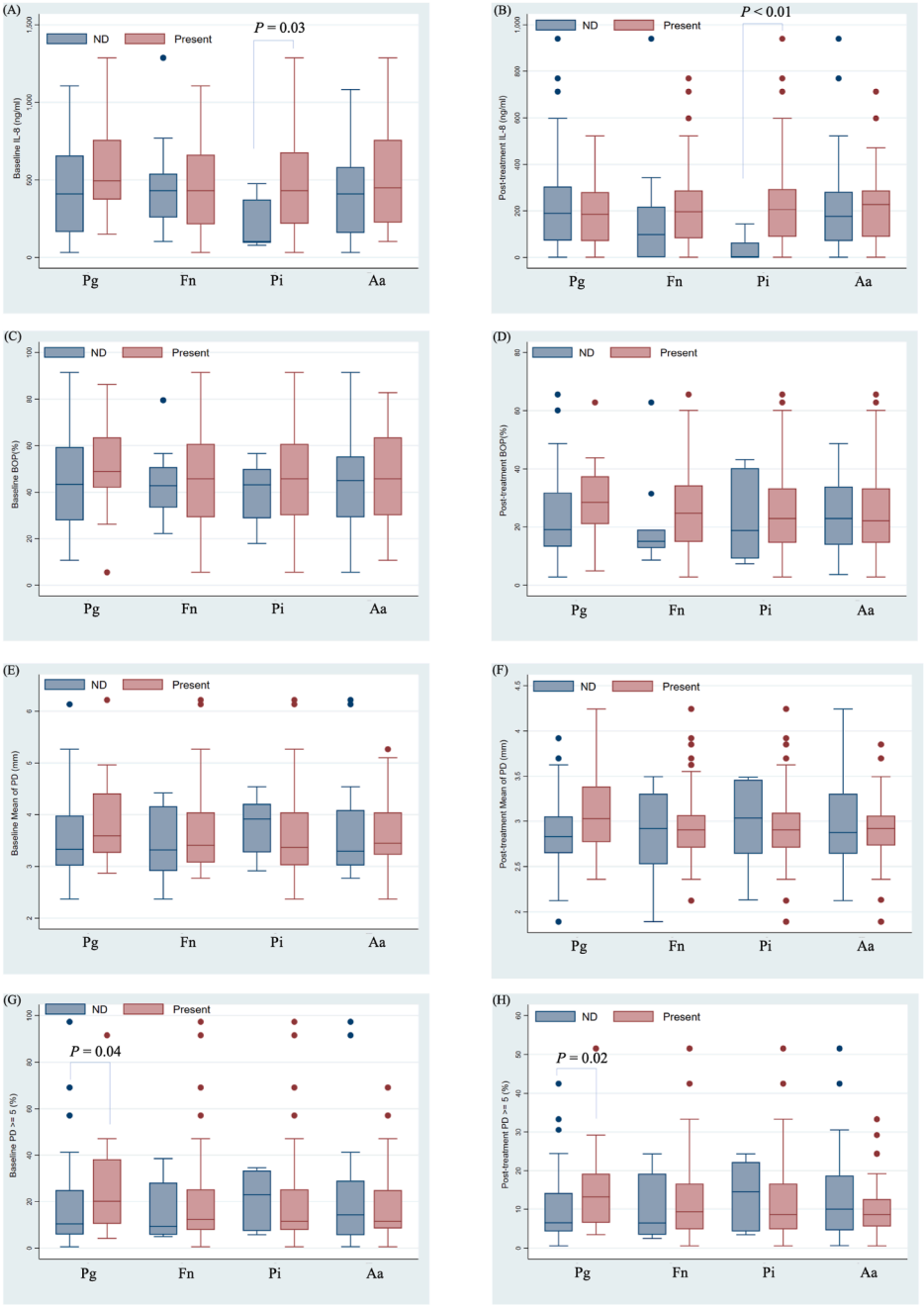

Figure 1 Distribution of IL-8 levels and periodontal clinical parameters according to bacterial presence. (A) Baseline IL-8 levels; (B) Post-treatment IL-8 levels; (C) Baseline bleeding on probing (BOP, %); (D) Post-treatment BOP (%); (E) Baseline mean probing depth (PD, mm); (F) Post-treatment mean PD (mm); (G) Baseline percentage of sites with PD $\geq$ 5 mm; (H) Post-treatment percentage of sites with PD $\geq$ 5 mm. Data were analyzed using the Mann—Whitney U test. Pg: *P. gingivalis*; Fn: *F. nucleatum*; Pi: *P. intermedia*; Aa: *A. actinomycetemcomitans*.

persisted one month after treatment (median 205.70 vs. 1.06 ng/mL; Fig. 1B, $P < 0.01$). Participants with *P. gingivalis* had significantly higher baseline and post-treatment percentages of sites with PD $\geq$ 5 mm compared with those without infection (baseline median: 20.22 % vs. 10.39 %, Fig. 1G, $P = 0.04$; post-treatment median: 13.24 % vs. 6.49 %, Fig. 1H, $P = 0.02$).

Fig. 1 shows that *P. intermedia* infection was associated with higher salivary IL-8 levels, while *P. gingivalis* infection correlated with a higher percentage of sites with PD $\geq$ 5 mm. As 17 of 18 *P. gingivalis*-infected participants were also co-infected with *P. intermedia*, we further assessed the combined effects of both pathogens on IL-8 and PD $\geq$ 5 mm.

Table 2 shows the distribution of salivary IL-8 levels and PD $\geq$ 5 mm percentage by *P. gingivalis* and *P. intermedia* status. As only one participant was infected with *P. gingivalis* but not *P. intermedia*, this case was excluded from

Table 2 Distribution of salivary IL-8 levels and percentage of sites with PD ≥ 5 mm by *P. gingivalis* and *P. intermedia* status.

Baseline Pathogens		N	IL-8		PD ≥ 5 mm (%)	
			Baseline	Post treatment	Baseline	Post treatment
P. gingivalis	*P. intermedia*		Median (Q1-Q3)		Median (Q1-Q3)	
ND	ND	4	98.44 (86.14–289.28)	1.06 (1.06–32.38)	20.38 (6.58–33.96)	13.27 (3.88–23.26)
ND	Present	52	415.41 (193.88–670.28)	206.86 (94.67–328.82)[a]	10.39 (5.78–23.11)	6.50 (4.46–12.52)
Present	ND	1	374.92 (374.92–374.92)	143.52 (143.52–143.52)	23.00 (23–23)	14.58 (14.58–14.58)
Present	Present	17	508.65 (410.19–758.04)[a]	195.66 (70.55–281.29)[a]	19.75 (10.42–38.24)	11.9 (6.52–19.23)
Kruskal–Wallis test			$P = 0.04$	$P = 0.02$	$P = 0.14$	$P = 0.07$

Q1: first quartile; Q3: third quartile; ND: not detected.
[a] Significant compared with participants without *P. gingivalis*/*P. intermedia* by Bonferroni post hoc test.

statistical analysis. Participants without infection of either pathogen had significantly lower baseline IL-8 levels compared with those co-infected with both pathogens (98.44 vs. 508.65 ng/mL, $P = 0.03$). After treatment, IL-8 levels remained significantly lower in participants without either pathogen than in those infected with *P. intermedia* alone (1.06 vs. 206.86 ng/mL, $P = 0.01$) or co-infected with both *P. gingivalis* and *P. intermedia* (1.06 vs. 195.66 ng/mL, $P = 0.04$). However, the percentage of sites with PD ≥ 5 mm was not affected by co-infection with *P. gingivalis* and *P. intermedia*.

Of the 18 participants with *P. gingivalis*, 16 were co-infected with *P. intermedia* and *F. nucleatum*. Because *P. gingivalis*, *F. nucleatum*, and *P. intermedia* frequently co-occurred, whereas *A. actinomycetemcomitans* did not consistently cluster with them, subsequent analyses focused on the combined effects of *P. gingivalis* and *A. actinomycetemcomitans* on SRP prognosis. To clarify pathogen combinations associated with prognosis, Table 3 presents regression analyses of specific periodontal profiles and adjusted risk factors for the percentage of sites with post-treatment PD ≥ 5 mm. In the univariate model, participants with *P. gingivalis* showed a higher percentage of sites with PD ≥ 5 mm (5.26 %) compared to those without. To further investigate the independent association of *P. gingivalis* and residual PD ≥ 5 mm, Models I–III sequentially adjusted for IL-8, smoking status, and oral health behaviors. In Model I, after adjusting for IL-8, *P. gingivalis* was associated with 4.41 % increased of percentage of sites with PD ≥ 5 mm, without significance. In Model II, *P. gingivalis* significantly associated with an increased percentage of post-treatment PD ≥ 5 mm (5.11 %, $P < 0.05$). However, in Model III, with further adjustment for oral health behaviors, the association persisted (4.32 %) but lost statistical significance. These findings suggest that the association between *P. gingivalis* and residual PD ≥ 5 mm may be modified by smoking and attenuated by IL-8 levels and oral health behaviors.

Participants infected with *P. gingivalis* but not *A. actinomycetemcomitans* had a 9.72 % higher percentage of PD ≥ 5 mm compared with those without either pathogen ($P < 0.05$), whereas co-infection was associated with a slight, non-significant increase (1.35 %). To further investigate the independent associations of baseline *P.*

Table 3 Regression of the specific periodontal pathogen profiles and adjusted risk factor percentage of sites with PD ≥ 5 mm.

Dependent variable			Post-treatment PD ≥ 5 mm (%)							
Independent variable										
Pathogens		N	Univariate		Model I		Model II		Model III	
P. gingivali			β	SE	β	SE	β	SE	β	SE
ND		56	1.00	–	1.00	–	1.00	–	1.00	–
Present		18	5.26	2.60	4.41	2.52	4.85	2.36*	4.32	2.42
P. gingivalis	*A. actinomycetemcomitans*									
ND	ND	29	1.00	–	1.00	–	1.00	–	1.00	–
ND	Present	27	−0.39	2.54	−1.51	2.48	−1.47	2.27	−1.57	2.29
Present	ND	8	9.72	3.79*	7.99	3.71*	8.05	3.39*	7.83	3.42*
Present	Present	10	1.35	1.35	−0.30	3.41	0.18	3.12	−0.49	3.22

β: beta coefficient. SE: standard error of beta.
*$P < 0.05$. ND, not detected.
Model I: Adjusted for baseline IL-8.
Model II: Adjusted for baseline IL-8 and smoking status.
Model III: Adjusted for baseline IL-8, smoking status, and oral health behavior (tooth brushing frequency and dental visits).

gingivalis/*A. actinomycetemcomitans* with residual PD $\geq$ 5 mm percentage, In Model I (adjusted for IL-8), participants with *P. gingivalis* but not *A. actinomycetemcomitans* again had a higher percentage of PD $\geq$ 5 mm (7.99 %, $P < 0.05$), while co-infection with both bacteria was associated with a slight, non-significant reduction (−0.30 %). These patterns remained consistent after additional adjustment for smoking status (Model II). After adjusting for IL-8, smoking status, and oral health behaviors, baseline *P. gingivalis* infection without *A. actinomycetemcomitans* was associated with a higher percentage of residual PD $\geq$ 5 mm (7.83 %, $P < 0.05$), whereas co-infection with *A. actinomycetemcomitans* attenuated this association (−0.49 %), showing a non-significant decreasing trend (Model III).

Discussion

Residual periodontal sites with PD $\geq$ 5 mm after SRP are important indicators of periodontitis progression and tooth loss.[20] In the present study, multivariate logistic regression showed a significant association between *P. gingivalis* detection and the proportion of residual PD $\geq$ 5 mm. Even when including a second periodontal pathogen, *P. gingivalis* remained a significant risk factor for poor response to periodontitis treatment post one month. This aligns with previous findings by Fujise et al., who reported its utility in assessing periodontitis treatment outcome.[2]

Mechanistically, *P. gingivalis* can induce IL-8 secretion in periodontal tissues,[4] although elevated salivary IL-8 may also reflect the presence of other oral pathogens.[21] This interaction may partly explain the observed relationship between baseline *P. gingivalis*, IL-8 levels and SRP treatment prognosis. Collectively, our findings suggest that among the tested bacteria, *P. gingivalis* may represent the most important pathogen contributing to periodontal tissue destruction.

Lipopolysaccharide (LPS) from *P. intermedia* and *P. gingivalis*, along with other bacterial components, can induce IL-8 expression in saliva, leading to the development of periodontitis.[4,22] *P. intermedia* might coaggregate with *P. gingivalis*, contributing to dental plaque formation, synergistically forming a nutrient-sharing system as pathogens.[8,22] In our cohort, 93 % of participants had *P. intermedia*, while *P. gingivalis* was only present in some cases. The present study shows that patients with baseline *P. intermedia* had significantly higher salivary IL-8 levels than those without (data not shown), suggesting a synergistic effect between *P. intermedia* and *P. gingivalis* in elevating salivary IL-8 levels.

Participants exhibited varied distributions of *P. gingivalis*, *F. nucleatum*, *P. intermedia*, and *A. actinomycetemcomitans*, all pathogens common in periodontitis.[21] Notably, *P. gingivalis* and *A. actinomycetemcomitans* were rarely detected together. While *F. nucleatum* co-adheres with *P. gingivalis* during disease progression,[7] *P. gingivalis* can suppress invasion of gingival epithelial cells by coinfecting *F. nucleatum*.[23] Additionally, during biofilm formation, *P. gingivalis* exerts a competitive advantage over *A. actinomycetemcomitans*, thus affecting the development of periodontitis.[9]

In vitro biofilm models suggest that *P. gingivalis* and *A. actinomycetemcomitans* may be incompatible within the same plaque biofilm. Conversely, *P. intermedia* frequently coaggregates with *P. gingivalis*, reinforcing their combined role in periodontitis development.[8,22]

This study has several limitations. First, the absence of post-treatment pathogen data limited direct evaluation of bacterial reduction and interaction with IL-8, though baseline bacterial presence still provided predictive insights for prognosis. Second, the analysis was limited to only four periodontal pathogens. Even so, the inclusion of key pathogens and salivary IL-8 levels at baseline provides valuable evidence for predicting clinical treatment prognosis to non-surgical periodontal therapy and for informing host—microbe—based strategies to enhance treatment efficacy. Finally, the relatively small sample size, short follow-up period, and reliance on salivary IL-8 without systemic or gingival tissue biomarkers limit the generalizability of the results. Future studies with larger sample size, extended follow-up, incorporation of systemic and gingival tissue biomarkers, and expanded microbial profiling are warranted to confirm the role of specific pathogen interactions and their modulation of salivary cytokine responses in long-term treatment outcomes.

In conclusion, *P. gingivalis* was associated with residual PD $\geq$ 5 mm after non-surgical periodontal therapy. Although *P. gingivalis* co-infection with *A. actinomycetemcomitans* showed no significant effect on PD, the trend remained noteworthy. By integrating both microbial and host inflammatory dimensions, this study provides novel insights into the multifactorial determinants of periodontal treatment outcomes beyond what has been reported in biomarker-only studies. The added value of our work in elucidating hots—microbe interactions, thereby differentiating the present study from prior investigation that examined IL-8 or single pathogens in isolation. Specifically, we highlight how the combined assessment of multiple pathogens and salivary IL-8 offers a more comprehensive understanding of the effects on treatment prognosis. The findings not only suggest strategies to improve the prognosis of SRP but also highlight the potential of salivary IL-8 and microbial profiling to inform the future development of chair-side diagnostic tools for risk stratification.

Declaration of competing interest

The authors have declared that there are no competing interests.

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