


Oral Microbiota Variations in Psoriasis Patients Without Comorbidity

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Background: Psoriasis is a chronic inflammatory skin disease, and its etiology is still unclear. There is increasing evidence suggesting that microorganisms may trigger psoriasis. However, the relationship between psoriasis and oral microbiota remains poorly understood. Our aim is to identify differences in the composition and diversity of the oral microbiota between patients with psoriasis and healthy controls, and to discover oral microbial markers for assessing the severity of psoriasis.

Methods: This study recruited 20 psoriasis patients and 20 healthy individuals, collecting their saliva to analyze the composition of the oral microbiota in psoriasis patients. We employed 16S rRNA sequencing technology and utilized various methods for oral microbiome analysis, including the Shannon Index, Gini-Simpson Index, Principal Coordinates Analysis (PCoA), non-metric multi-dimensional scaling (NMDS), Linear discriminant analysis Effect Size (LEfSe), Wilcoxon test, and Spearman's rank correlation.

Results: The results showed that the alpha diversity of oral microbiota was higher in psoriasis patients. The relative abundances of certain bacterial taxa differed between psoriasis and healthy individuals, including *Prevotella*, *Prevotella 7* and *Porphyromonas gingivalis*, which are increased in psoriasis. We also found a positive correlation between *Alloprevotella*, *Porphyromonas*, and *Neisseria* with the severity of psoriasis, while *Veillonella* showed a negative correlation.

Conclusion: In summary, this study found significant changes in the composition of the oral microbiota in patients with psoriasis. Some oral bacteria are associated with psoriasis severity. It provides a new perspective on the relationship between the oral microbiota and psoriasis.

Keywords: psoriasis, oral microbiota, dysbiosis, comorbidity, 16s rRNA

Introduction

Psoriasis is an inflammatory skin disease that poses a significant global disease burden,¹ affecting approximately 125 million individuals worldwide.² Characterized by scaly skin plaques, joint pain, and nail abnormalities, psoriasis extends beyond skin involvement. It often comes with various comorbidities, making it a complex disease with significant systemic effects.³ Additionally, psoriasis patients frequently smoke, and there is always a presence of subclinical inflammation of the airways, which complicates the disease further.⁴ The pathogenesis of psoriasis includes factors such as genetic susceptibility, immune dysfunction, infection, and environmental influences.⁵ Recently, the potential role of the microbiota in psoriasis development and progression has garnered increasing attention.⁶ The term "microbiota" refers to the collective microorganisms inhabiting human body surfaces and cavities. Researches have demonstrated that the microbiota critically influences immune function and inflammation regulation,⁷ key elements in the pathogenesis of psoriasis.⁵

While prior studies have established the role of gut microbiota in the pathogenesis of psoriasis,⁸ the potential significance of the oral microbiota remains largely unexplored. Serving as a significant microbiota reservoir, the oral cavity and its microbiota have been linked to the pathogenesis of various systemic diseases, like atherosclerosis,⁹ type 2

diabetes mellitus,¹⁰ hypertension,¹¹ systemic lupus erythematosus,¹² and rheumatoid arthritis.¹³ Recently, the investigation of the intricate relationship between oral microbiota and psoriasis has gained attention. In their study, Orozco-Molina et al¹⁴ found a difference in the subgingival microbiota composition between patients with plaque psoriasis and healthy individuals. Additionally, they noted increased levels of inflammatory markers in the saliva samples from these patients. Belstrøm et al¹⁵ identified a correlation between psoriasis and both the salivary microbiota and levels of inflammation-related proteins in saliva. While these studies hint at the potential influence of the oral microbiota on psoriasis, no research to date has assessed the composition of oral microbiota in psoriasis patients lacking concurrent systemic diseases. Furthermore, no research to date has examined the link between oral microbiota and the severity of psoriasis using high-throughput sequencing methods. Lastly, considering the variety in populations, methods, subpopulations, and geographic regions, a broader range of evidence is required to enhance our understanding of the link between the oral microbiota and psoriasis. Therefore, we carried out this research in Chinese population.

In this study, we explored the oral microbiota in patients with psoriasis, employing 16S rRNA sequencing technology and contrasting it with a healthy control group. Moreover, we carried out a correlation analysis between the oral microbiota and the severity indicators of psoriasis. Our goal was to discern differences in the composition and diversity of the oral microbiota between patients with psoriasis and the healthy controls and to spot oral microbial markers for assessing the severity of psoriasis. In conclusion, the primary objective of this study was to provide novel insights into the relationship between psoriasis and oral microbiota, and further lay a foundation for the treatment of psoriasis-associated oral microbiota.

Materials and Methods

Participants

The design of this study is based on prospective specimen collection followed by a retrospective evaluation. This study recruited a total of 40 participants, including 20 patients diagnosed with psoriasis and 20 healthy individuals. From May 2023 to July 2023, a three-month period, 20 patients diagnosed with plaque psoriasis were recruited from the Dermatology Outpatient Clinic at the Second Affiliated Hospital of Xi'an Jiaotong University. Additionally, 20 healthy individuals were also recruited during the same period.

The inclusion criteria for our study were that participants must be diagnosed with plaque psoriasis by two dermatologists, aged between 18 and 60 years old, and belong to the Chinese Han population. The exclusion criteria included individuals who have taken antibiotics or probiotics within the last three months, those who are pregnant or breastfeeding, and those with coexisting autoimmune diseases, diabetes, obesity, neurological or psychiatric disorders, or infectious diseases. Additionally, individuals who received corticosteroids or any immunosuppressive drugs within the past three months were also excluded.

Collection of Saliva Samples

Patients were informed to fast and avoid drinking water for at least two hours before saliva collection, as well as to refrain from smoking, chewing gum, or engaging in exercise. Using a 50mL sterile centrifuge tube, 1mL of non-stimulated saliva was collected from both psoriasis patients and healthy controls, then transferred to sterile cryogenic vials using a sterile pipette tip. Samples were transported to the laboratory in a refrigerated container within two hours of collection and stored at -80°C until further analysis.

DNA Extraction and Amplicon Sequencing

DNA extraction was performed using the TGuide S96 Magnetic Soil/Stool DNA Kit from Tiangen Biotech (Beijing) Co., Ltd., adhering strictly to the protocols provided by the manufacturer. Nucleic acid concentration was measured using a microplate reader (Synergy HTX, GeneCompang Limited) by adding 1X dsDNA HS Working Solution (Yisheng Biotechnology Co., Ltd., Shanghai).

We utilized the universal primer set 27F: AGRGTTTGATYNTGGCTCAG and 1492R: TASGGHTACCTTGTTASGACTT to amplify the full-length 16S rRNA gene from the genomic DNA extracted from each sample. Both the forward and reverse 16S

primers were tagged with sample-specific PacBio barcode sequences for multiplexed sequencing. We opted for barcoded primers because they reduce chimera formation compared to protocols where primers are added in a second PCR reaction. The KOD One PCR Master Mix from TOYOBO Life Science was used to carry out 25 cycles of PCR amplification, starting with an initial denaturation at 95°C for 2 minutes, followed by 25 cycles of denaturation at 98°C for 10 seconds, annealing at 55°C for 30 seconds, and extension at 72°C for 1 minute 30 seconds, with a final step at 72°C for 2 minutes. PCR amplicons were purified using Agencourt AMPure XP Beads from Beckman Coulter (Indianapolis, IN) and quantified using the Qubit dsDNA HS Assay Kit and Qubit 4.0 Fluorometer from Invitrogen (Thermo Fisher Scientific, Oregon, USA). After quantification, amplicons were pooled in equal amounts. SMRTbell libraries were prepared from the amplified DNA using the SMRTbell Express Template Prep Kit 2.0 according to the manufacturer's instructions (Pacific Biosciences). Purified SMRTbell libraries from the pooled and barcoded samples were sequenced on a single PacBio Sequel II 8M cell using the Sequel II Sequencing Kit 2.0.

Bioinformatic Analysis

The bioinformatics analysis for this study was conducted using BMK Cloud (Biomarker Technologies Co., Ltd., Beijing, China). The raw reads from sequencing were filtered and demultiplexed using the SMRT Link software (version 8.0) with settings of minPasses ≥ 5 and minPredictedAccuracy ≥ 0.9 to obtain circular consensus sequencing (CCS) reads. Subsequently, lima (version 1.7.0) was used to assign the CCS sequences to the corresponding samples based on their barcodes. CCS reads that contained no primers and those beyond the length range of 1,200–1,650 bp were discarded using forward and reverse primer recognition and the Cutadapt quality control process (version 2.7). The UCHIME algorithm (version 8.1) was utilized to detect and remove chimera sequences to ensure clean reads. Sequences with similarity $\geq 97\%$ were clustered into the same operational taxonomic unit (OTU) using USEARCH (version 10.0), and OTUs with fewer than three sequence reads were filtered out. Taxonomy annotation for OTUs was performed using a combination of the Naive Bayes classifier and BLAST, employing the SILVA database (release 138). Alpha diversity was calculated and displayed using QIIME2 and R software, respectively. Beta diversity was assessed to evaluate the similarity of microbial communities from different samples using QIIME. Principal coordinate analysis (PCoA) and non-metric multidimensional scaling (NMDS) were applied to analyze beta diversity. Additionally, Linear Discriminant Analysis (LDA) effect size (LEfSe) was used to test significant taxonomic differences among groups, with a logarithmic LDA score threshold set at 4.0.

Statistical Analysis

Numerical data are presented as mean \pm standard deviation for normally distributed data or median with interquartile range for non-normally distributed continuous variables. Categorical variables are presented as numbers (%). Wilcoxon test was performed to analyze data that remained non-normally distributed even after logarithmic transformation. Spearman's rank correlation coefficient was used to assess the correlation between bacterial abundance and clinical features. All significance tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Participants

We recruited a total of 40 participants, comprising 20 psoriasis patients (7 females and 13 males) and 20 healthy individuals (8 females and 12 males). No significant differences were observed between the two groups regarding gender, age, and body mass index (BMI). Notably, none of the participants had any autoimmune or chronic diseases. [Table 1](#) presents the specific clinical characteristics of all subjects.

Microbial Characteristics of Oral Cavity in Psoriasis

Following the sequencing and barcode identification of 40 samples, we obtained a total of 513,453 circular consensus sequence (CCS) reads. Each sample produced a minimum of 8,482 CCS sequences, averaging 12,836 CCS sequences per sample. Across all samples, 745 OTUs were detected, including 632 OTUs in psoriasis patients and 727 OTUs in the healthy control group ([Figure 1A](#)).

Table 1 Clinical Characteristics of Psoriasis Patients and Healthy Subjects

Clinical Indices	Psoriasis Patients	Healthy Subjects	P
Gender (female/male)	7/13	8/12	0.107
Age (years)	29.5±3.5	28.5±2.0	0.254
Body Mass Index (Kg/m ²)	22.7±3.1	23.2±2.4	0.571
Disease duration (month)	107.9±17.3	/	/
Age of Pso onset (years)	20.7±1.5	/	/
Itch	10/10	/	/
PASI	3.9 (2.7,12.0)	/	/
PGA	2.0 (2.0,3.0)	/	/
BSA	5.0 (3.0,12.8)	/	/

Abbreviations: PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; BSA, Body Surface Area; Pso, psoriasis.

The stabilization of the OTU abundance curve of the sample indicates that the biodiversity within the sample has been adequately covered by the applied sequencing depth ([Supplement Figure 1](#)). After evaluating the quality of sequencing data, we used alpha diversity to assess both richness and uniformity of microbial communities in the two study groups. According to the Gini-Simpson index, there was higher species diversity in the psoriasis group than in the healthy control group ($p < 0.05$, [Figure 1B](#)). While not statistically significant, the Shannon Index pointed to a heightened alpha diversity in psoriasis patients compared to healthy controls ([Figure 1C](#)). These findings suggest that psoriasis could affect the diversity of the oral microbiota.

The beta diversity of the two population groups was assessed using multiple parameters. The PCoA based on weighted UniFrac dissimilarity and non-metric multidimensional scaling (NMDS) using weighted UniFrac dissimilarity indicated differences in community structure between the two groups ($p < 0.05$, [Figure 1D](#) and [E](#)) These results suggested that the oral microbiota composition of psoriasis patients may differ from the healthy control group.

Different Composition in Oral Microbiota Between Psoriasis Patients and Healthy Subjects

Due to the differences in community structure between the two groups, we employed multiple methods to further explore specific differential bacteria at different taxonomic levels.

We compared the taxonomic groups between the psoriasis group and the healthy control group and visualized the results using bar graphs. At the phylum and genus levels, the composition and relative abundance of oral microbiota in both study groups are depicted ([Figure 2A](#) and [B](#)). We also presented a histogram of species distribution in each sample ([Supplement Figure 2](#)).

At the phylum level, in the healthy control group, *Firmicutes* (42.54%) dominates as the most abundant phylum, followed by *Proteobacteria* (26.39%), *Bacteroidetes* (18.72%), *Fusobacteriota* (5.61%), and *Actinobacteriota* (3.31%). In contrast, the psoriasis patient group exhibits the following proportions: *Firmicutes* (37.98%), *Bacteroidetes* (27.69%), *Proteobacteria* (20.4%), *Fusobacteriota* (6.56%), and *Patescibacteria* (4.1%). In the group of psoriasis patients, there is an increase in the proportion of *Bacteroidetes* and a decrease in the proportion of *Proteobacteria*.

At the genus level, in the healthy control group, the predominant genera in the oral microbiota included *Streptococcus* (23.1%), *Neisseria* (12.48%), *Haemophilus* (11.97%), *Veillonella* (5.64%), and *Prevotella_7* (5.18%). In the psoriasis patient group, the dominant genera are the same as in the healthy control group, but there are differences in the proportional abundance of each genus: *Streptococcus* (17.29%), *Neisseria* (10.42%), *Prevotella_7* (10.18%), *Haemophilus* (9%), and *Veillonella* (6.46%).

Furthermore, using the Wilcoxon rank-sum test, we identified and confirmed differential bacteria between the two groups.

At the phylum level, differences were observed in the relative abundances of *Patescibacteria*, *Bacteroidota*, *Actinobacteriota*, and *Proteobacteria* between the two groups ($p < 0.05$).

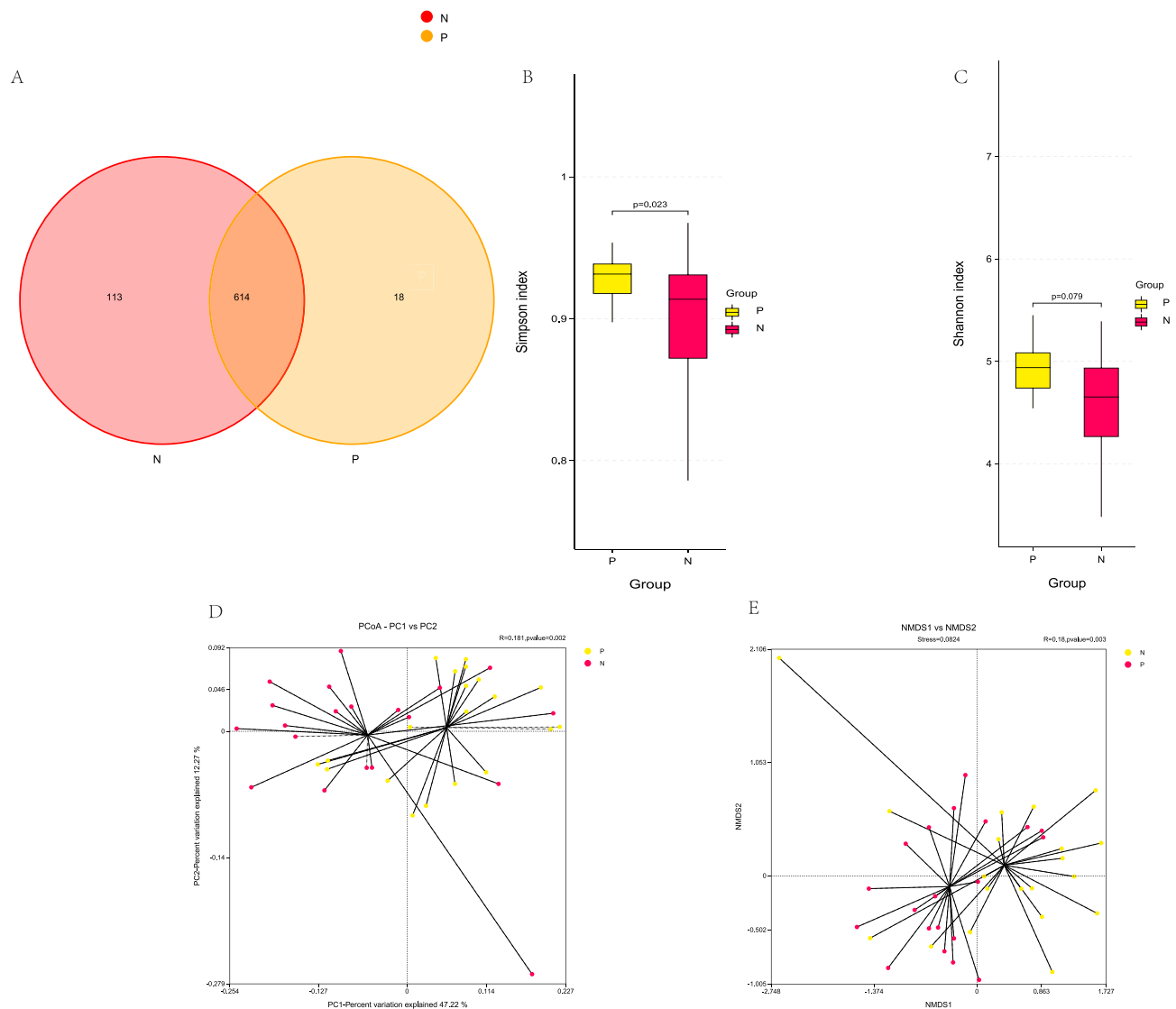


Figure 1 The similarity and differences in oral microbiota between the psoriasis group and the healthy control group. Venn diagram showing the unique and shared operational taxonomic unit (OUT) in psoriasis and healthy control group (A), alpha Diversity comparisons based on the Simpson index (B) and Shannon Index (C), beta Diversity comparisons based on the PCoA (D) and NMDS (E). P, Psoriasis patients; N, Healthy subjects.

At the genus level, significant differences in the relative abundance of *Prevotella*, *Prevotella_7*, *Porphyromonas*, and *Haemophilus* were observed between the two study groups ($p < 0.05$, Figure 3A–D).

At the species level, differences were observed for *Porphyromonas_gingivalis*, *Cenchrus_americanus*, *Prevotella_pallens*, and *Porphyromonas_pasteri* between the two groups ($p < 0.05$).

Potential Oral Bacterial Biomarkers for Psoriasis

We utilized the LefSe analysis (LDA score > 4.0 , $p < 0.05$) to identify potential oral microbiota biomarkers associated with psoriasis. In psoriasis patients, significant enrichments were found in *Bacteroidetes*, *Patascibacteriota*, *Bacteroidia*, *Bacteroidales*, *Prevotellaceae*, *Porphyromonadaceae*, *Alloprevola*, *Porphyromonas*, *Prevotella_7*, and *Prevotella_melaninogenica*. Meanwhile, *Proteobacteria*, *Gammaproteobacteria*, *Enterobacterales*, *Pasteurellaceae*, and *Haemophilus* showed significant enrichment in the healthy control group (Figure 4, $p < 0.05$).

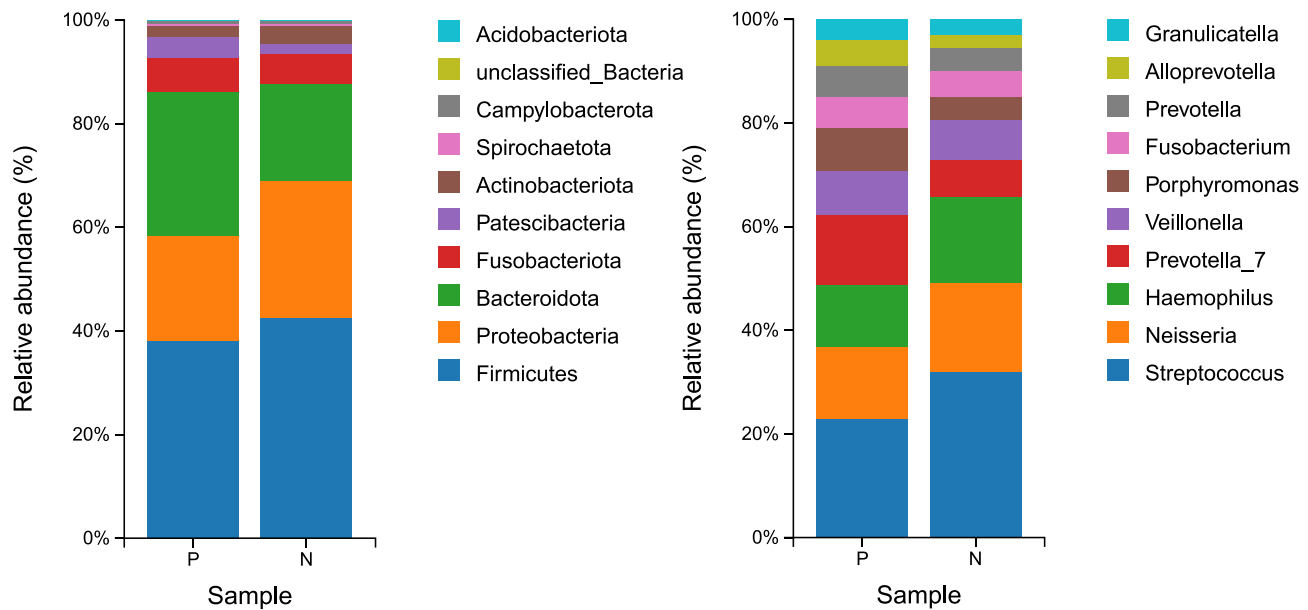


Figure 2 The relative abundance of oral microbiota at the phylum (left) and genus (right) levels in the psoriasis group and the healthy control group. P, Psoriasis patients; N, Healthy subjects.

Correlation Between Oral Microbiota and the Severity of Psoriasis

We conducted Spearman correlation analysis to explore the relationship between the top 10 ranked bacteria at the genus level in oral microbiota of psoriasis patients and their Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA), and Body Surface Area (BSA) scores. We observed positive correlations between *Alloprevotella*, *Porphyromonas*, *Neisseria*, and BSA, PASI, PGA, respectively. On the other hand, *Veillonella* showed a negative correlation with PGA (Figure 5, $p < 0.05$). The specific values of these clinical indicators are shown in [Supplement Table 1](#).

Discussion

The primary aim of this research was to explore the oral microbiota composition in uncomplicated Chinese psoriasis patients, contrast it with a healthy control group, and uncover potential factors within the oral microbiota that might be linked to the severity of psoriasis.

This study revealed that psoriasis patients exhibit higher alpha diversity in their oral microbiota than the healthy control group, indicating greater richness and evenness within this group. This observation is in line with alterations in oral microbiota noted in various inflammatory diseases, including rheumatoid arthritis and systemic lupus erythematosus.^{12,16} Contrarily, research by Belstrøm et al¹⁵ reported no significant differences in alpha diversity between the groups, a disparity potentially due to varying sequencing methodologies, population attributes, and racial backgrounds. Therefore, more research is required to validate the disparities in oral microbial diversity in psoriasis patients. Beta diversity analysis, employed to assess the similarity between two sample groups, uncovered significant differences in microbial community structures between our two groups. This observation corresponds with the specific differences seen in the subsequent oral microbiota analysis. Altogether, these results imply a potential role of the oral microbiota in psoriasis pathogenesis.

Subsequently, We proceeded to uncover specific variations in the oral microbiota across the two groups. Specifically, at the phylum level, an increase in Bacteroidetes and a decrease in Proteobacteria were noted; this rise in Bacteroidetes is attributed to an upsurge in *Prevotella_7* and *Prevotella*. More specifically, the distinctive patterns of oral microbiota distribution in the psoriasis group included an increase in the relative abundances of *Prevotella*, *Prevotella a_7*, and *Porphyromonas gingivalis*, coupled with a decrease in *Haemophilus*. Previous research has shown that changes in the skin and gut microbiota play a crucial role in inflammatory skin diseases.^{17,18} Interestingly, some studies suggest that topical medications may exert their effects through interactions with the microbiome.¹⁹ Additionally, findings indicate that the combination of medications with nanomaterials can enhance the treatment efficacy for psoriasis, potentially due

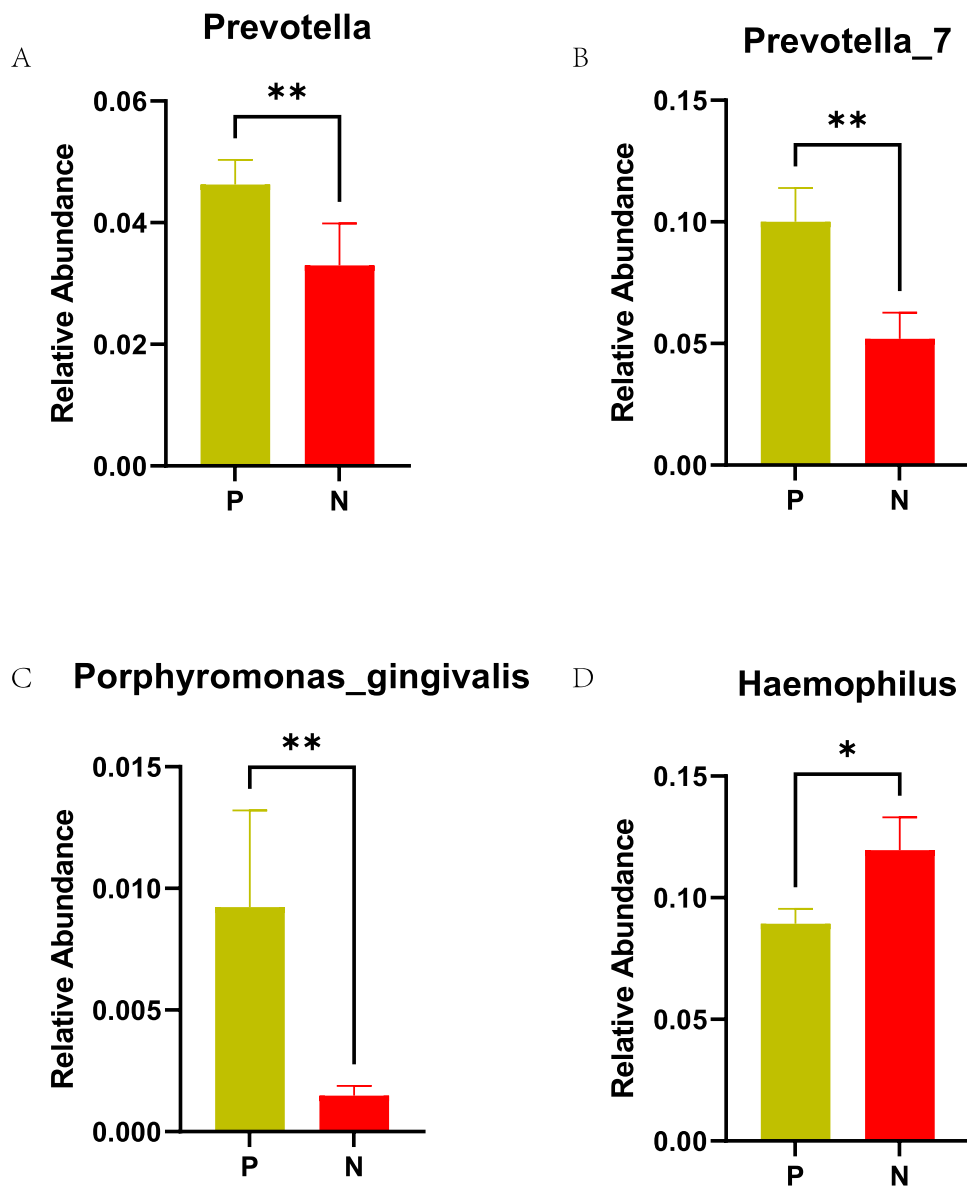


Figure 3 The differences in relative abundance of *Prevotella* (A), *Prevotella_7* (B), *Porphyromonas gingivalis* (C) and *Haemophilus* (D) between the psoriasis group and the healthy control group. P, Psoriasis patients; N, Healthy subjects.

Notes: *P<0.05, **P<0.01.

to alterations in the microbiome, which merits further investigation.²⁰ Overall, these discoveries underscore the vital importance of the microbiome in maintaining human health. Consequently, we speculate that changes in the oral microbiota might influence chronic inflammatory conditions such as psoriasis.

Numerous studies indicate that a rise in *Prevotella* abundance correlates with various local and systemic diseases such as periodontitis,²¹ bacterial vaginosis,²² and rheumatoid arthritis,²³ among others. *Prevotella* primarily activates Toll-like receptor 2, leading to the production of Th17 polarizing cytokines, including interleukin 23 (IL-23) and IL-1, by antigen-presenting cells. Subsequently, IL-23 activates Th17 cells to generate an inflammatory response.²⁴ Researches had shown that the activation of Th17 cells is a key component in the pathogenesis of psoriasis.⁵ Strikingly, in this study, a significant increase in the relative abundance of *Prevotella* was observed in the psoriasis group. Therefore, it can be inferred that *Prevotella* may play a role in the immune dysregulation associated of psoriasis.

In rheumatoid arthritis, peptide arginine deiminase produced by *Porphyromonas gingivalis* disrupts the balance of the antigen/antibody complex, causing the body to produce citrullinated antibodies against its own antigens.²⁵ Additionally,

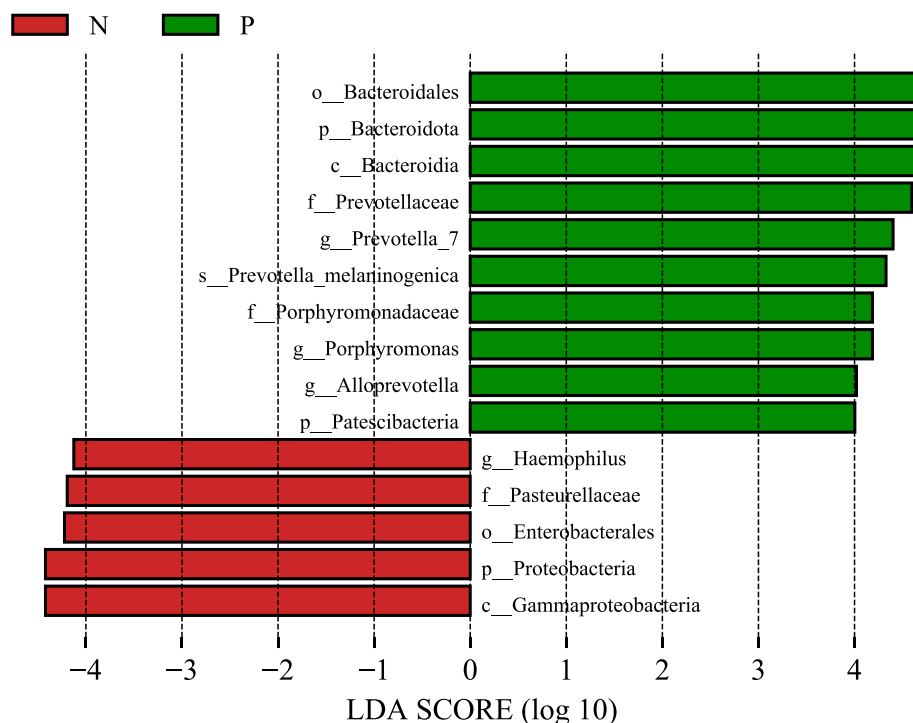


Figure 4 The LEfSe analysis of the psoriasis group and the healthy control group. P, Psoriasis patients; N, Healthy subjects.

animal studies have reported that *Porphyromonas gingivalis* can exacerbate ulcerative colitis,²⁶ an inflammatory disease with genetic and immune factors similar to psoriasis. Moreover, Previous studies have suggested that periodontitis may trigger or exacerbate psoriasis,²⁷ and *Porphyromonas gingivalis* is a pathogenic bacterium associated with periodontitis.²⁸ This implies that *Porphyromonas gingivalis* may promote the occurrence and progression of psoriasis by influencing inflammatory responses.

An observed decrease in the abundance of *Haemophilus* has been noted among individuals with rheumatoid arthritis, showing an inverse correlation with serum anti-citrullinated protein antibody (ACPA) levels.²⁹ Rheumatoid arthritis, similar to psoriasis, is a systemic inflammatory disease having comparable underlying pathogenic mechanisms. Moreover, changes in *Haemophilus* as seen in pustular psoriasis patients align with the outcomes of our study.³⁰ Consequently, we conjecture that *Haemophilus* could contribute to the immune dysregulation related to psoriasis, including its other subtypes. To sum up, these observations imply that specific bacteria might participate in the pathogenesis of psoriasis.

The LEfSe analysis has identified numerous potential biomarkers for psoriasis, providing new perspectives into its diagnosis and treatment strategies. Divergences in *Porphyromonas*, *Prevotella_7*, and *Haemophilus* levels were additionally affirmed between the two groups. Nevertheless, more comprehensive research is crucial to confirm these outcomes and shed light on the intricate mechanisms through which the oral microbiome impacts psoriasis development.

One unique aspect of this study was the correlation analysis between oral microbiota abundance and the severity of psoriasis. It was found that *Alloprevotella*, *Porphyromonas*, and *Neisseria* showed a positive correlation with disease severity, while *Veillonella* exhibited a negative correlation with disease severity. The upregulation of *Alloprevotella* expression in diarrheal irritable bowel syndrome suggests that *Alloprevotella* may have pro-inflammatory effects.³¹ *Porphyromonas*, as a common oral pathogenic bacterium, is associated with various diseases.^{32–34} We speculate that higher abundance of *Porphyromonas* may exacerbate local inflammation in the oral cavity, and subsequently affect the severity of psoriasis through bloodstream or the gut. *Veillonella* is a known propionate-producer³⁵ and propionic acid has been shown to possess significant anti-inflammatory effects in various disease. We hypothesized that a reduction in the abundance of oral *Veillonella* among psoriasis patients may lead to a partial decrease in propionic acid levels, thereby exacerbating the severity of psoriasis. The correlation unveiled

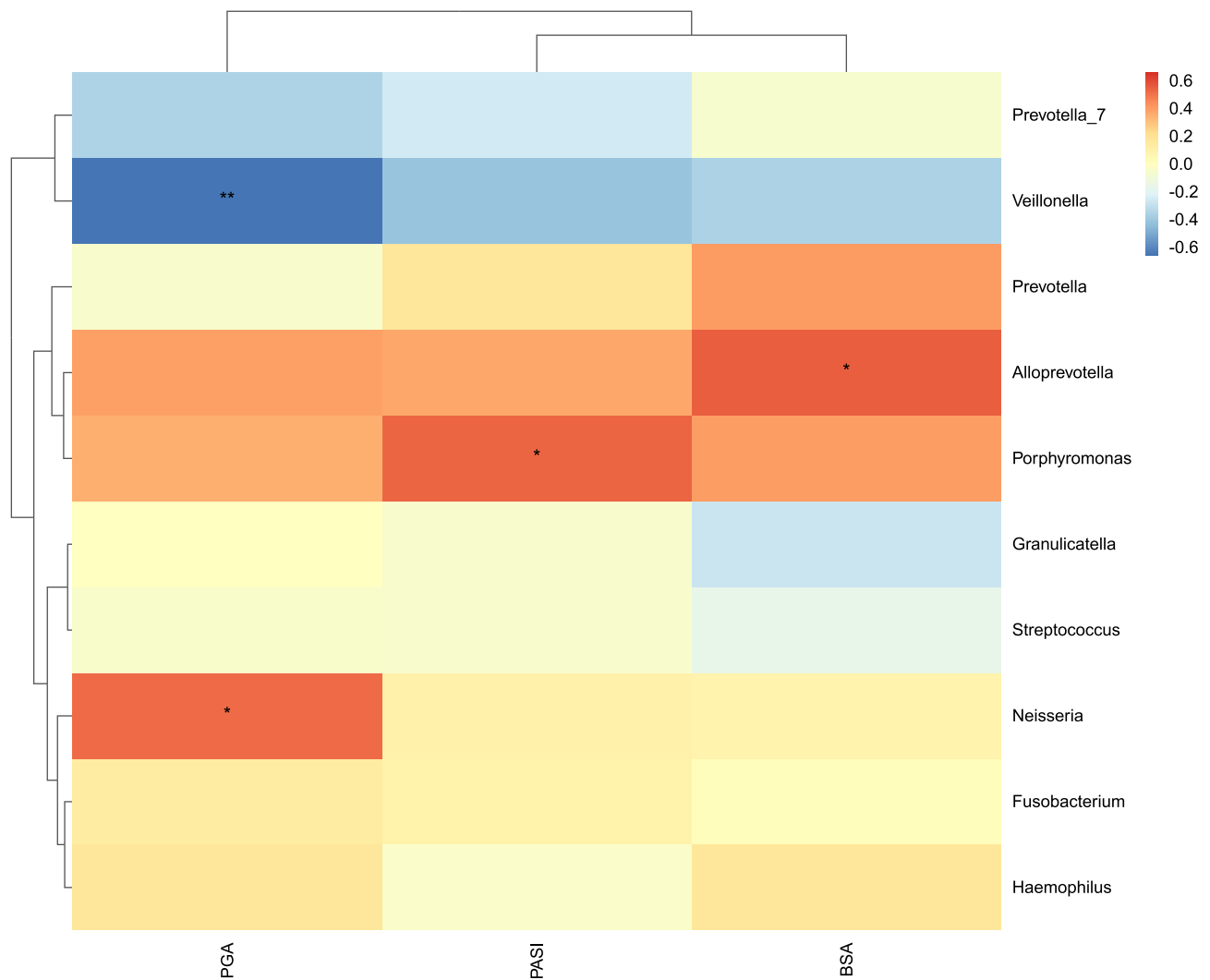


Figure 5 Spearman correlation analysis was conducted to assess the correlation between the severity of psoriasis and the oral microbiota at the genus level.

Notes: * $P < 0.05$, ** $P < 0.01$.

Abbreviations: PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; BSA, Body Surface Area.

between oral microbiota and psoriasis severity indicators provides further evidence supporting the role of oral microbiota in psoriasis pathogenesis.

Although this study offered a new perspective on understanding the pathogenesis of psoriasis, there are some limitations to consider. Firstly, the study included a relatively small number of patients. However, based on the analysis of the final data, the results remain reliable. Secondly, the functional analysis of differentially abundant bacteria between the two groups was not conducted in this study. It should be noted that this was an initial exploration, and future research may employ metagenomic approaches to further investigate bacterial functionality. Lastly, due to the absence of collaboration with dental experts, no oral examinations were administered to the study participants. Consequently, participants were included in the study without prior oral diagnosis, regardless of whether they had dental caries or periodontitis. Future investigations should consider subgroup analysis based on oral conditions for more comprehensive insights.

Conclusion

In conclusion, our study reveals the relative abundance of the oral microbiota in patients with psoriasis, indicating dysbiosis in the oral microbiota of psoriasis patients. We have identified potential biomarkers such as *Prevotella* and *Porphyromonas* and established a relationship between *Porphyromonas* and the severity of psoriasis. These findings

provide preliminary evidence of the involvement of oral microbiota in the immunopathogenesis of psoriasis. Further experimentation is required to investigate the specific mechanisms and roles of oral microbiota in psoriasis pathogenesis.

Data Sharing Statement

The datasets generated for this study can be found in the SRA accession database: ID PRJNA1060843. <https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1060843>.

Ethics Declarations

This study complies with the ethical standards of the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University, approval number 2023471. All participants provided written informed consent prior to their participation.

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Author Contributions

Kaidi Zhao and Yang Zhao have contributed equally to this work and share first authorship. Shengxiang Xiao and Chen Tu share last authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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