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Insights into the blood, gut, and oral microbiomes in Chinese patients with myocardial infarction: a case-control study

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Abstract

Background Emerging evidence suggests that changes in the blood microbes might be associated with cardiovascular disease, especially myocardial infarction (MI). However, some researchers are questioning whether a true "blood microbiome" actually exists. They hypothesized that these microbes may translocate into the bloodstream from the gut or oral cavities. To test this hypothesis, we analyzed the microbial composition, diversity, and potential role in disease progression by comparing blood, gut, and oral microbiota profiles in a cohort of MI patients and healthy controls.

Methods In this study, 144 samples, including blood, fecal, and saliva, were collected from twenty-four myocardial infarction patients and twenty-four healthy controls. These samples were analyzed using 16 S rRNA sequencing to characterize the microbial profiles across the three distinct microbial compartments. Differential analyses were conducted to find key differential microbiota for MI. Spearman's rank correlation analysis was used to study the association between microbiota and clinical indicators.

Results Our findings revealed striking microbial shifts across blood, gut, and oral compartments in MI patients compared to healthy controls. In the blood, we observed significant enrichment of the phyla Armatimonadota and Caldatribacteriota, alongside the genera *Bacillus*, *Pedobacter*, and *Odoribacter*. The gut microbiota of MI patients showed a notable increase in the phyla Proteobacteria, Verrucomicrobiota, Cyanobacteria, Synergistota, and Crenarchaeota, as well as the genera *Eubacterium_coprostanoligenes_group*, *Rothia*, *Akkermansia*, *Lachnospiraceae_NK4A136_ group*, and *Eubacterium_ruminantium_group*. Meanwhile, the oral microbiota of MI patients was uniquely enriched with the phylum Elusimicrobiota and the genera *Streptococcus*, *Rothia*, and *Granulicatella*. These distinct microbial signatures highlight compartment-specific alterations that may play a role in the pathophysiology of MI. Additionally, LEfSe analysis identified 64 distinct taxa that differed across the three compartments. Of these, eight taxa were unique to blood, eighteen to the gut, and thirty-eight to the oral microbiota, all of which demonstrated

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significant associations with clinical markers of MI. Functional pathways were predicted and analyzed via KEGG annotation, but no statistically significant differences were found between MI patients and healthy controls in any of the microbiome compartments.

Conclusion This study demonstrates significant alterations in the blood, gut, and oral microbiome profiles of MI patients, identifying specific bacterial taxa strongly associated with key markers of myocardial infarction. The unique microbial patterns detected in the blood provide compelling evidence for the existence of a stable core blood microbiome, highlighting its importance as a key contributor to cardiovascular health and disease progression.

Keywords Myocardial infarction, Microbiota, Dysbiosis, Correlation, Biomarkers

Introduction

Acute myocardial infarction (AMI) is a critical cardiac emergency with profound morbidity and mortality. As a major driver of heart failure and cardiac death globally, it remains a pressing public health challenge requiring urgent attention and advanced therapeutic strategies [1]. Although percutaneous coronary intervention (PCI) has significantly reduced AMI-related mortality, there is still a crucial need for advanced strategies to further enhance therapeutic outcomes [2]. Recent studies suggest that the gut microbiome is a dynamic environmental factor that may contribute to AMI development [3] and serve as a promising therapeutic target [4]. Similarly, evidence indicates a link between oral microbiota and AMI, with serum antibody levels against various oral pathogens showing a positive correlation with myocardial infarction risk [5]. Polymerase chain reaction (PCR) and microbial sequencing technologies also detected oral microbial DNA in coronary artery thrombi of myocardial infarction patients, including both periodontal and non-periodontal pathogenic bacteria [6, 7], suggesting a potential relationship between oral bacteria and coronary artery thrombus formation in AMI. Periodontitis induced by the disruption of oral microbial ecology has been documented to raise the risk of AMI [8]. However, to date, no single study has directly compared the bacterial diversity evident in the blood, gut, and oral microbiomes of healthy individuals and MI patients. Therefore, the cross-site comparison is imperative because of the significant variability observed in microbiota across different subjects [9, 10]. Reducing infarct size and preserving heart function is vital to lowering mortality and preventing heart failure, underscoring the need to uncover new therapeutic targets and unravel disease mechanisms.

Epidemiological studies provide evidence to support the link between chronic infections and the risk of cardiovascular disorders [11, 12]. Oral diseases are specifically linked to an increased risk of MI [13–15], whereas recent research has directly correlated the metabolic activity of the gut microbiome with blood pressure levels [16–18]. Multiple studies suggest that CVD-associated bacteria originate from the gut and oral sources in the blood [19, 20]. These studies suggest that elevated permeability of the gut barrier and induced absorbent of the gut mucosa led to the translocation of gut microorganisms into the bloodstream [21, 22]. This process triggers excessive immune inflammation, potentially heightening the risk of cardiovascular events [19, 20]. In the last six years, there has been notable interest in exploring the concept of a blood microbiome in healthy controls and its potential implications for health and disease [23–25]. Traditionally, blood was considered a sterile habitat, whereas sporadic translocation and proliferation of the pathogens into the blood can trigger and disrupt the host response, which leads to severe health issues like sepsis, septic shock, or even death [26]. Moreover, asymptomatic transient bacteremia in blood donors is recognized as a significant contributor to transfusion-related sepsis [27].

Recent research has shed light on the presence of diverse microbial species in the bloodstream and their link to human diseases [28], such as type 2 diabetes [29, 30], colorectal cancer [31], hypertension [32], chronic kidney disease [33, 34], and MI [35–38], which has been well-documented. These results brought to light the possible influence of the blood microbiota on early diagnosis and disease discrimination. However, contrasting viewpoints have arisen, with some authors questioning the existence of a distinct blood microbiome. Instead, they suggest that microbes found in the blood originate from the gut (via the gut barrier) and oral cavity (via tooth infections) [19, 22, 23]. To address this question/hypothesis, it is essential to explore the microbiome signature of the blood and its relationship with both gut and oral microbiotas in patients with MI. This comprehensive approach would provide valuable insights into the origin and dynamics of blood-associated microbes and their potential role in the pathogenesis of MI and related conditions.

Previous studies have characterized the gut and oral bacterial signatures in patients with MI using cross-sectional designs. However, to date, no study has comprehensively analyzed the blood, gut, and oral microbiome composition in MI patients and healthy controls. This study aimed to investigate the blood microbiome and its composition relative to the gut and oral microbiomes of MI patients relative to those of healthy individuals. This

study provides insight into the comprehensive microbiome profile of MI patients, bridging the gap between blood, gut, and oral microbial communities. Understanding these interactions may uncover novel biomarkers and therapeutic targets for improved cardiovascular outcomes.

Materials and methods

Study design and subject recruitment

To examine the profiles of blood, gut, and oral microbiota in healthy and MI subjects, we enrolled 24 healthy individuals from the physical examination center and 24 patients with MI from the cardiology department of Gansu People's Hospital, Lanzhou, China. Inclusion criteria for both groups were as follows: Patients with confirmed MI and controls with no history of CVDs were selected. Exclusion criteria for both groups included participants with missing data, diabetes, kidney disease, gastrointestinal disorders, recent blood transfusions, pregnancy, inability to comply with sample collection, use of medications that could affect results (e.g., antibiotics, immunosuppressants), or oral diseases.

Demographic and clinical data collection

The demographic characteristics like age, height, weight, smoking, and alcohol habits, as well as the past medical history of the patients retrieved from the medical record system of the particular hospitals. Body mass index (BMI) was measured by (kg/cm^2), and systolic and diastolic blood pressure were recorded in millimeters of mercury (mmHg). Clinical data, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), fasting blood glucose (FBG), C-reactive protein (CRP), uric acid (UA), White blood cell (WBC) count, Red blood cell (RBC) count, Platelet (PLT) count, Hemoglobin (Hb), neutrophil count, serum creatinine (Scr), and pH were screened. These factors serve as covariates in exploratory statistical analyses, as many are recognized as potential confounders in various diagnoses related to atherosclerosis and thrombosis in CVD [11, 39].

Sample collection from three compartments

Clinically certified team members collected blood samples in Vacutainer EDTA tubes, following strict hygiene protocols. Medical staff wore lab coats, disposable gloves, and masks, and used sterilized reagents and materials to prevent contamination. A 5 ml blood sample was taken from each participant in the morning after overnight fasting and was immediately placed in a sterile centrifuge tube, then stored at -80 °C for further analysis.

Before saliva sample collection, patients rinsed their mouths with water. Then all the participants kept their mouths closed for about a minute to reduce contamination from microorganisms and food debris. A sterile saliva collection container was used to collect 3 to 5 ml of saliva from each participant. After collection, the saliva sample was immediately placed in a sterile centrifuge tube and stored at -80℃ for later analysis.

After collecting blood and saliva samples, participants received a stool collection kit with clear instructions for gathering fecal samples. Fecal samples were promptly delivered to the staff after defecation and temporarily stored in an ice box before being transported to the research laboratory. Upon arrival at the lab, the samples were initially frozen at -20 °C and then transferred to -80 °C for storage within 24 h.

DNA extraction and amplicon sequencing

According to manufacturer instructions, the DNA was extracted with the TGuide S96 Magnetic Soil /Stool DNA Kit (Tiangen Biotech Co., Ltd. Beijing). The DNA concentration of the samples was measured with the Qubit dsDNA HS Assay Kit and Qubit 4.0 Fluorometer (Invitrogen, Thermo Fisher Scientific, Oregon, USA).

The V3-V4 region of the 16 S rRNA gene was amplified from the DNA extracted from each sample using the universal primer set 338 F (5'-ACTCCTACGGGAGGCAGC A-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3'). The forward and reverse 16 S primers were tailed with sample-specific Illumina index sequences to allow for deep sequencing. The PCR was performed in a total reaction volume of 10 µl as follows: DNA template 5–50 ng, *Vn F (10µM) 0.3 µl, *Vn R (10µM) 0.3 µl, KOD FX Neo Buffer 5 µl, dNTP (2 mM each) 2 µl, KOD FX Neo 0.2 µl, ddH2O up to 10 µl. Vn F and Vn R are selected according to the amplification area. The PCR conditions were set as follows: initial denaturation at 95 °C for 5 min, followed by 25 cycles of denaturation at 95 °C for 30 s, annealing at 50 °C for 30 s, and extension at 72 °C for 40 s, and final step at 72 °C for 7 min. The total of PCR amplicons was purified with Agencourt AMPure XP Beads (Beckman Coulter, Indianapolis, IN) and quantified using the Qubit dsDNA HS Assay Kit and Qubit 4.0 Fluorometer (Invitrogen, Thermo Fisher Scientific, Oregon, USA). After the individual quantification step, amplicons were pooled in equal amounts. For the constructed library, use Illumina novaseq 6000 (Illumina, Santiago, CA, USA) for sequencing.

Bioinformatics and statistical analysis

The bioinformatics analysis of this study was performed with the aid of the BMK Cloud (Biomarker Technologies Co., Ltd., Beijing, China). According to the quality of a single nucleotide, raw data was primarily filtered by Trimmomatic (version 0.33). Identification and removal of primer sequences were processed by Cutadapt (version 1.9.1). Paired-end reads obtained from previous

steps were assembled by USEARCH (version 10) and followed by chimera removal using UCHIME (version 8.1). The high-quality reads generated from the above steps were used in the following analysis. Sequences with similarity ≥ 97% were clustered into the same operational taxonomic unit (OTU) by USEARCH (version 10.0), and the OTUs with abundance < 0.005% were filtered. Taxonomy annotation of the OTUs was performed based on the Naive Bayes classifier in QIIME2 using the SILVA database (release 132) with a confidence threshold of 70%. The Alpha diversity was calculated and displayed by the QIIME2 and R software, respectively. Beta diversity was determined to evaluate the degree of similarity of microbial communities from different samples using QIIME. Binary Jaccard-based Principal Coordinate Analysis (PCoA) and PERMANOVA were employed to assess beta diversity, highlighting similarities and differences among the blood, gut, and oral microbiota. Furthermore, we employed Linear Discriminant Analysis (LDA) effect size (LEfSe) to test the significant taxonomic difference among groups. A logarithmic LDA score of 4.0 was set as the threshold for discriminative features. The function prediction pathways of the blood, gut, and oral microbial community were predicted by Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt2) based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Spearman's correlation coefficients were used to assess associations between blood, gut, and oral microbiota and clinical parameters, with the results visualized using the R package "pheatmap."

Statistical analyses were performed using R (version 4.4.2), SPSS, GraphPad Prism (version 9.4.1), and Excel. Continuous variables were presented as mean ± standard deviation and pairwise comparisons were conducted using Fisher's exact test. The Mann-Whitney test was employed to assess quantitative differences. A P-value less than 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

The detailed baseline characteristics of MI patients and healthy controls are presented in Supplementary Table S1. Significant differences were observed in age, body mass index, hypertension, and alcohol consumption in the MI group compared to the controls. In contrast, no significant differences were found in sex, blood pH, smoking status, or diabetes mellitus between the two groups. As expected, the MI group exhibited elevated levels of low-density lipoprotein, triglycerides, blood glucose, C-reactive protein, white blood cell count, red blood cell count, neutrophils, and systolic blood pressure, alongside decreased levels of high-density lipoprotein compared to controls. These findings suggest a distinct metabolic and inflammatory profile in MI patients, characterized by dyslipidemia, heightened inflammatory markers, and altered blood pressure, highlighting key risk factors and potential diagnostic indicators for MI.

OTUs distribution across three distinct microbial compartments

A total of 11,235,623 raw sequencing reads were generated, of which 10,354,313 high-quality reads were retained following stringent filtration processes (average range: 40,430–71,905 reads per sample). Finally, 119,417 OTUs were identified across 144 samples encompassing blood, gut, and oral microbiota. Among the samples, the highest number of unique OTUs was observed in the blood (84,038), followed by saliva (16,144), while fecal samples exhibited the lowest number of unique OTUs (13,818). A total of 1,855 OTUs were shared between the blood and oral compartments, while 1,699 OTUs were detected in both the blood and gut compartments. Meanwhile, 611 OTUs were common between the oral and gut compartments. Notably, 1,252 OTUs were shared across all three compartments (Fig. 1A). These findings highlight distinct microbial diversity across blood, gut, and oral microbiota, with the blood exhibiting the highest unique OTUs. The shared OTUs suggest potential microbial exchange, particularly between the blood and oral compartments. The presence of a core microbiome across all three sites may play a key role in systemic health and disease regulation. Rarefaction curve analysis confirmed that the sequencing depth was adequate to comprehensively capture the microbial diversity within the samples (Fig. 1B).

Microbial diversity between patients and healthy groups across three distinct compartments

In terms of alpha diversity, the Chao1 index, which measures community richness, was lower in the blood microbiome of the MI group compared to the healthy (2221.85 vs. 2310.31, $p = 0.785$). In contrast, it was higher in both the gut (566 vs. 520, $p = 0.599$) and oral microbiome (676.19 vs. 664.75, $p = 0.889$) of MI patients (Fig. 1C). However, these differences were not statistically significant. Similarly, no significant differences were observed in the Shannon index, which reflects community diversity, for the blood (9.31 vs. 8.94, $p = 0.161$) and gut microbiome (5.75 vs. 5.75, $p = 0.986$). However, a significantly lower Shannon index was found in the oral microbiome of MI patients compared to the healthy group (5.95 vs. 6.32, $p = 0.03$) (Fig. 1D). The alpha diversity indices for the three microbial compartments are comprehensively summarized in Supplementary Table S2. These findings suggest that the blood, gut, and oral microbiomes exhibit distinct patterns of microbial richness and diversity, with a significantly lower diversity observed in

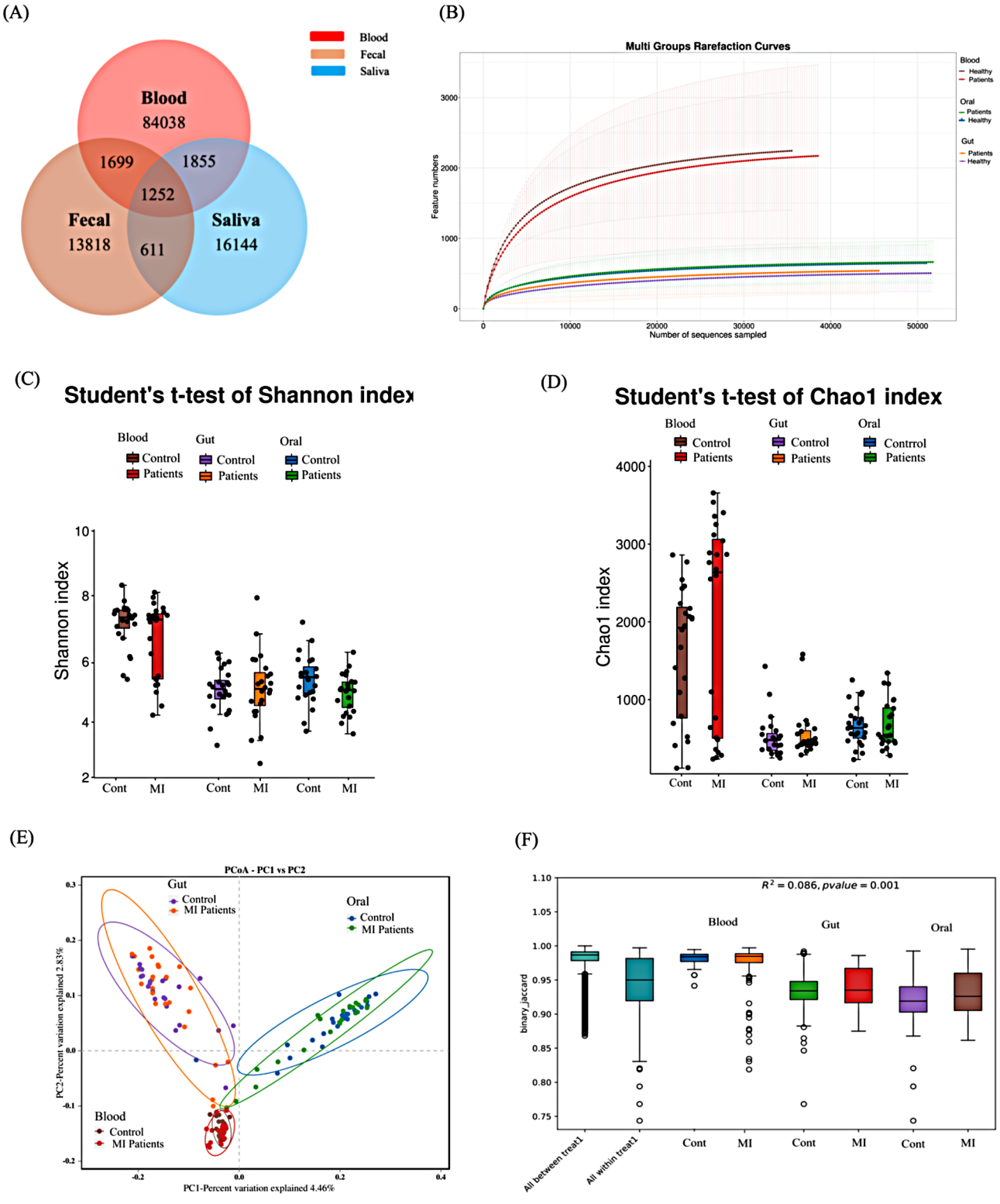

Fig. 1 (**A**) The Venn diagram depicts the unique and shared microbial OTUs across the blood, gut, and oral compartments. (**B**) The rarefaction curve illustrates species richness across both groups' blood, gut, and oral microbiota compartments. (**C**). Alpha diversity Chao1 index across three compartments (**D**). Alpha diversity Shannon index across three compartments. (**E**) Principal Coordinate Analysis (PCoA) based on the binary_Jaccard metric demonstrated a clear microbial community composition separation across distinct compartments of control and MI groups. (**F**) PERMANOVA analysis using the binary_Jaccard metric revealed significant differences in microbial community composition among distinct compartments

the oral microbiome of MI patients. Furthermore, beta diversity analysis was performed to assess the variation in the microbial communities of distinct compartments between both groups. Our results showed a clear separation into three distinct compartments based on the Bray-Curtis principal coordinate analysis (Fig. 1E), and PERMANOVA analysis ($R^2 = 0.239$; $p = 0.001$) validate significant differences across three compartments (Fig. 1F). These findings indicate that the microbial compositions and diversity of blood, gut, and oral microbiota are distinct, highlighting the unique microbial ecosystems associated with each microenvironment.

Relative abundance at the phylum and genus levels across three compartments

We first analyzed the abundance of phyla and their corresponding genera in the blood, gut, and oral microbiomes of the MI and control groups. Across all three compartments, the most prevalent phyla were Firmicutes, Bacteroidota, Proteobacteria, Actinobacteriota, and Fusobacteriota, as shown in Fig. 2. These findings suggest that the microbial composition of blood, gut, and oral microbiomes shares common dominant phyla, regardless of the compartment. However, potential differences in their relative abundance between the MI and control groups may indicate a role of microbiome dysbiosis in MI pathophysiology.

To investigate the microbial profiles associated with MI, we characterized the blood, gut, and oral microbiota, revealing distinct compositional differences between MI and control groups. The blood microbiome profile at phyla levels between both groups revealed that Firmicutes (25% vs. 22%) and Bacteroidota (19% vs. 15%) were enriched in the MI group, while Proteobacteria (20.13% vs. 23.5%), Actinobacteria (5% vs. 6%), Thermotogota (4% vs. 5%), Acidobacteriota (2% vs. 3%), and Verrucomicrobiota (1% vs. 2%) were depleted in MI compared to control group. Similarly, the gut microbiota

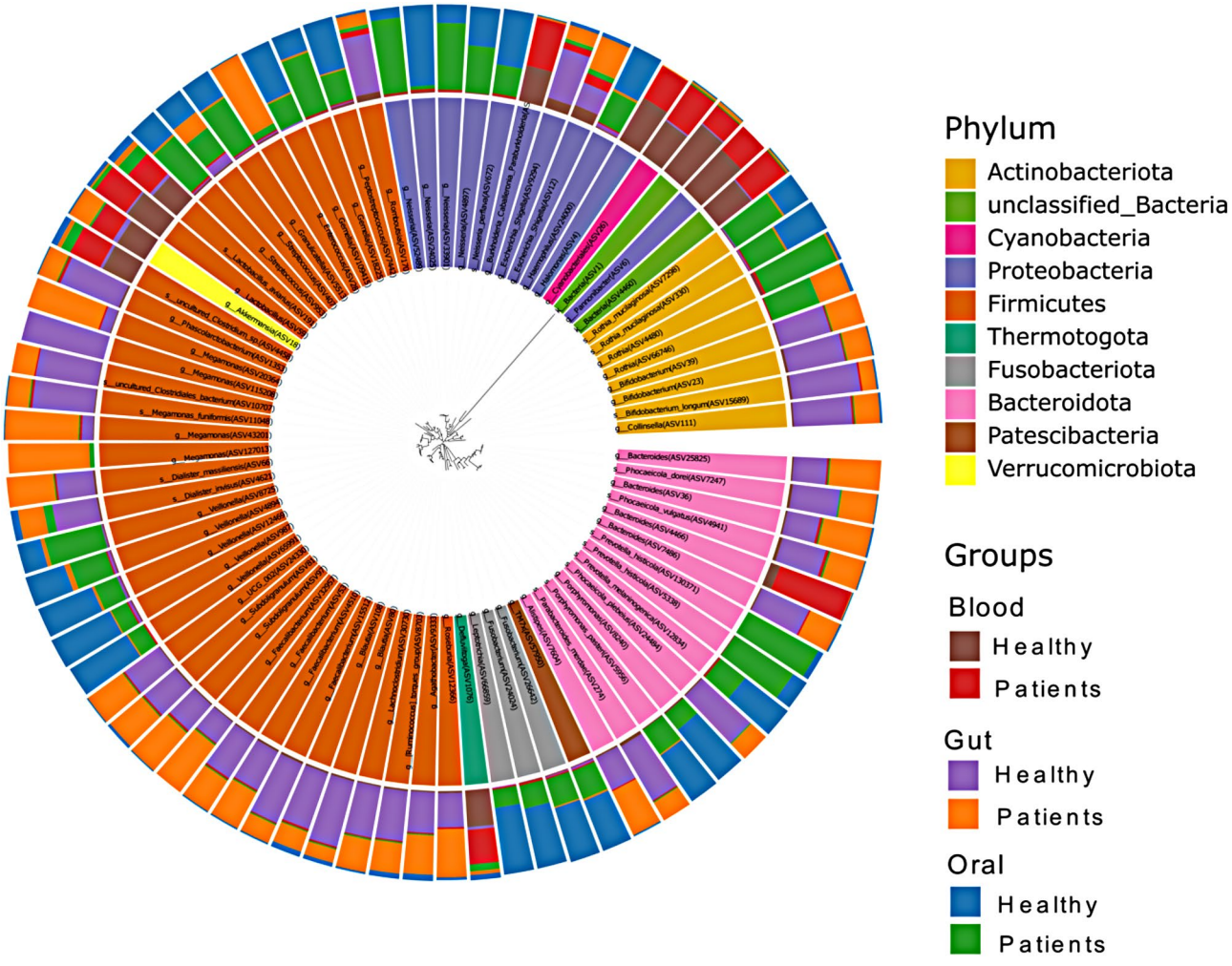

Fig. 2 The blood, gut, and oral microbiomes are represented in a phylogenetic tree, illustrating the predominant phyla and their corresponding genera across all compartments

showed increased levels of Bacteroidota (22.87% vs. 21.56%) and Proteobacteria (11% vs. 8%), with reduced proportions of Firmicutes (55.97% vs. 60.41%) and Actinobacteriota (5% vs. 7%). In the oral microbiota, the MI group exhibited enrichment of Firmicutes (39% vs. 36%), Proteobacteria (17% vs. 14%), Actinobacteria (12% vs. 9%), and Fusobacteriota (5% vs. 1%), while Bacteroidota (18% vs. 21%), Patescibacteria (2% vs. 3%), and Spirochaetota (2% vs. 1%) were depleted compared to the control group. These findings underscore the distinct alterations in microbial composition across blood, gut, and oral microbiota in the context of MI (Fig. 3A).

At the genus level, significant differences were observed in the microbial profiles of the MI group compared to controls. In the blood microbiota, *Bacteroides* was the most prevalent genus in the MI group (3% vs. 1%), while *Defluviitoga* (4% vs. 5%) and *Escherichia_Shigella* (1% vs. 2%) were depleted. In the gut microbiota, the MI group showed enrichment of *Bacteroides* (11% vs. 10%), *Subdoligranulum* (6% vs. 4%), *Escherichia_Shigella* (5% vs. 4%), and *Parabacteroides* (4% vs. 2%), while *Faecalibacterium* (7% vs. 8%), *Bifidobacterium* (2% vs. 5%), and *Blautia* (1% vs. 4%) were depleted. In the oral microbiota, *Streptococcus* was the most abundant genus in the MI group (18% vs. 12%), followed by *Neisseria* (9% vs. 6%), *Rothia* (9% vs. 4%), and *Prevotella_7* (7% vs. 5%). However, the MI group exhibited reduced levels of *Veillonella* (5% vs. 7%), *Haemophilus* (4% vs. 5%), *Porphyromonas* (3% vs. 5%), *Prevotella* (3% vs. 4%), *Fusobacterium* (2% vs. 5%), and *Leptotrichia* (2% vs. 5%) (Fig. 3B). These findings indicate significant microbial dysbiosis in the blood, gut, and oral microbiota of the MI group compared to controls. Enrichment of specific phyla and genera, such as *Bacteroides* in blood and gut and *Streptococcus* in oral microbiota, alongside the depletion of beneficial taxa like *Faecalibacterium* and *Bifidobacterium*, suggests a shift in microbial composition associated with MI. These alterations highlight the potential role of microbiota in the pathogenesis and progression of MI.

Blood Microbiome alterations in MI patients at phylum and genus levels

We conducted the Wilcoxon rank-sum test to identify significant differences in blood microbial composition between MI and HC groups. The analysis revealed ten phyla and twenty genera with distinct abundances between the two groups. Among them, the phyla Armatimonadota and Caldatribacteriota were significantly enriched in MI patients, while Proteobacteria, Actinobacteria, Patescibacteria, Spirochaetota, Fusobacteriota, Fibrobacterota, Hydrothermarchaeota, and Caldisericota were significantly depleted compared to the healthy group ($p < 0.05$; Fig. 4).

At the genus level, *Bacillus*, *Pedobacter*, and *Odoribacter* were enriched in the MI group, and *Halomonas*, *Pannonibacter*, *Streptococcus*, *Acinetobacter*, unclassified_Vicinamibacterales, *Treponema*, *Alloprevotella*, *Bifidobacterium*, *RB41*, unclassified_Alphaproteobacteria, *Corynebacterium*, *Dubosiella*, *Desulfovibrio*, *Faecalibacterium*, uncultured_rumen_bacterium, *Allobaculum*, and *Prevotella* were significantly depleted compared to the healthy group ($p < 0.05$; Fig. 5).

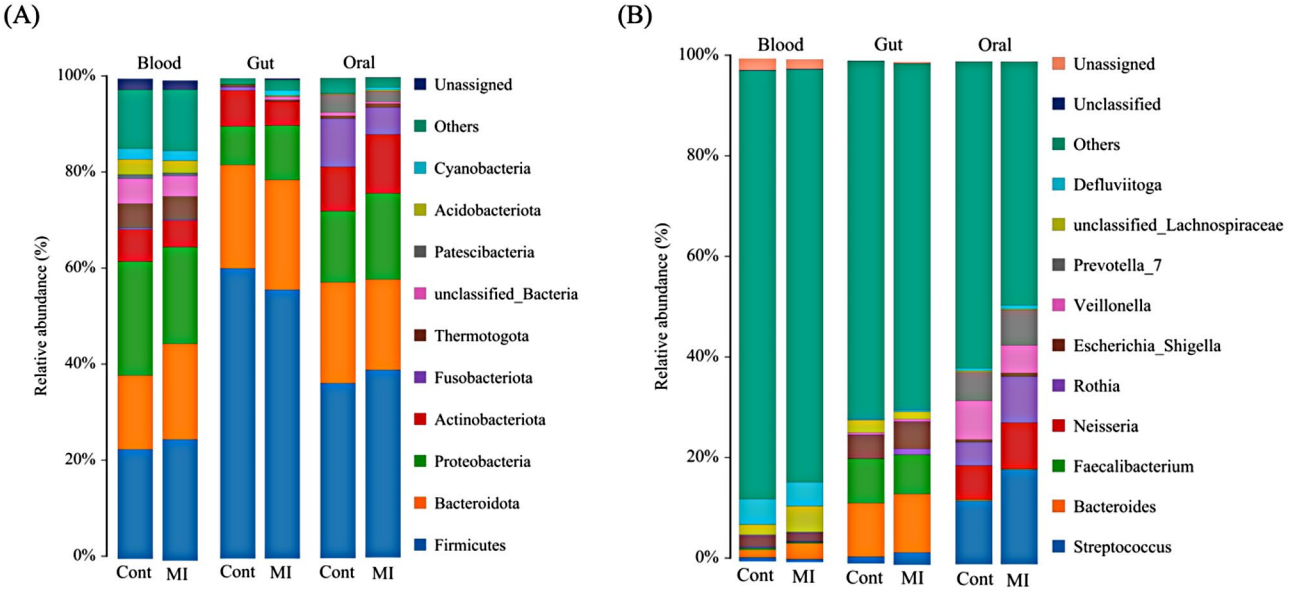

Fig. 3 The relative abundance of microbial communities at both the phylum and genus levels varies across blood, gut, and oral compartments, with each phylum and genus distinctly associated with a specific compartment. (**A**) The phylum-level relative abundance across the three compartments between the MI and Control groups. (**B**) The genus-level relative abundance across the three compartments between both groups

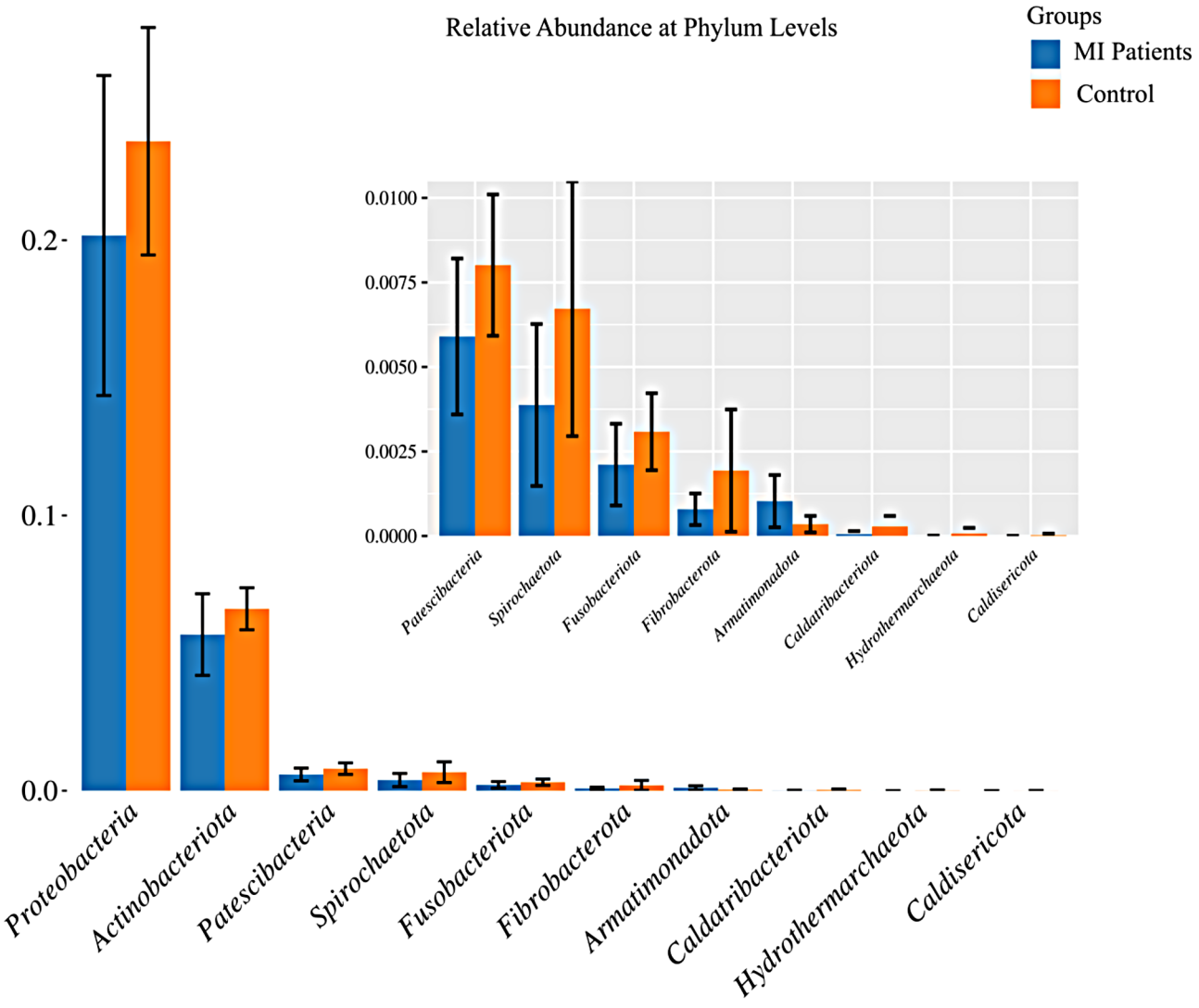

Fig. 4 The Wilcoxon rank-sum test was used to identify significant differences in blood microbial taxa between MI and control groups. Boxplots illustrate these differences at the bacterial phylum level in both groups

Gut Microbiome alterations in MI patients at phylum and genus levels

As fecal microbiota serves as a proxy for gut microbiota, we examined bacterial diversity in fecal samples to ascertain potential differences in gut microbiota between patients and control groups. The gut microbiota analysis revealed six phyla and twenty genera with distinct abundances between the two groups. The MI group exhibited a significant enrichment of the phyla Proteobacteria, Verrucomicrobiota, Cyanobacteria, Synergistota, and Crenarchaeota, while Actinobacteria was significantly depleted compared to the healthy group ($p < 0.05$; Fig. 6).

At the genus level, *Rothia*, *Akkermansia*, *Lachnospiraceae_NK4A136_group*, and *Eubacterium_ ruminantium_group* were significantly enriched in the MI group, whereas *Bifidobacterium*, *Blautia*, *Romboutsia*, *Roseburia*, *Coprococcus*, *Clostridium_sensu_stricto_1*, *Dorea*, *Eubacterium_halli_group*, *Fusicatenibacter*, *Butyricicoccus*, *Ruminococcus_ gnavus_ group*, *Anaerostipes*, and *Tyzzerella* were significantly depleted compared to the healthy group ($p < 0.05$; Fig. 7).

Oral Microbiome alterations in MI patients at phylum and genus levels

Subsequently, the oral microbiota analysis revealed four phyla and twenty genera with distinct abundances between the two groups. Among them, phylum Elusimicrobiota was significantly enriched, and Fusobacteriota, Campylobacterota, and Latescibacterota were significantly depleted in the MI group compared to the control ($p < 0.05$; Fig. 8).

At the genus level, *Streptococcus*, *Rothia*, and *Granulicatella* were significantly enriched in the MI group, and *Veillonella*, *Porphyromonas*, *Fusobacterium*,

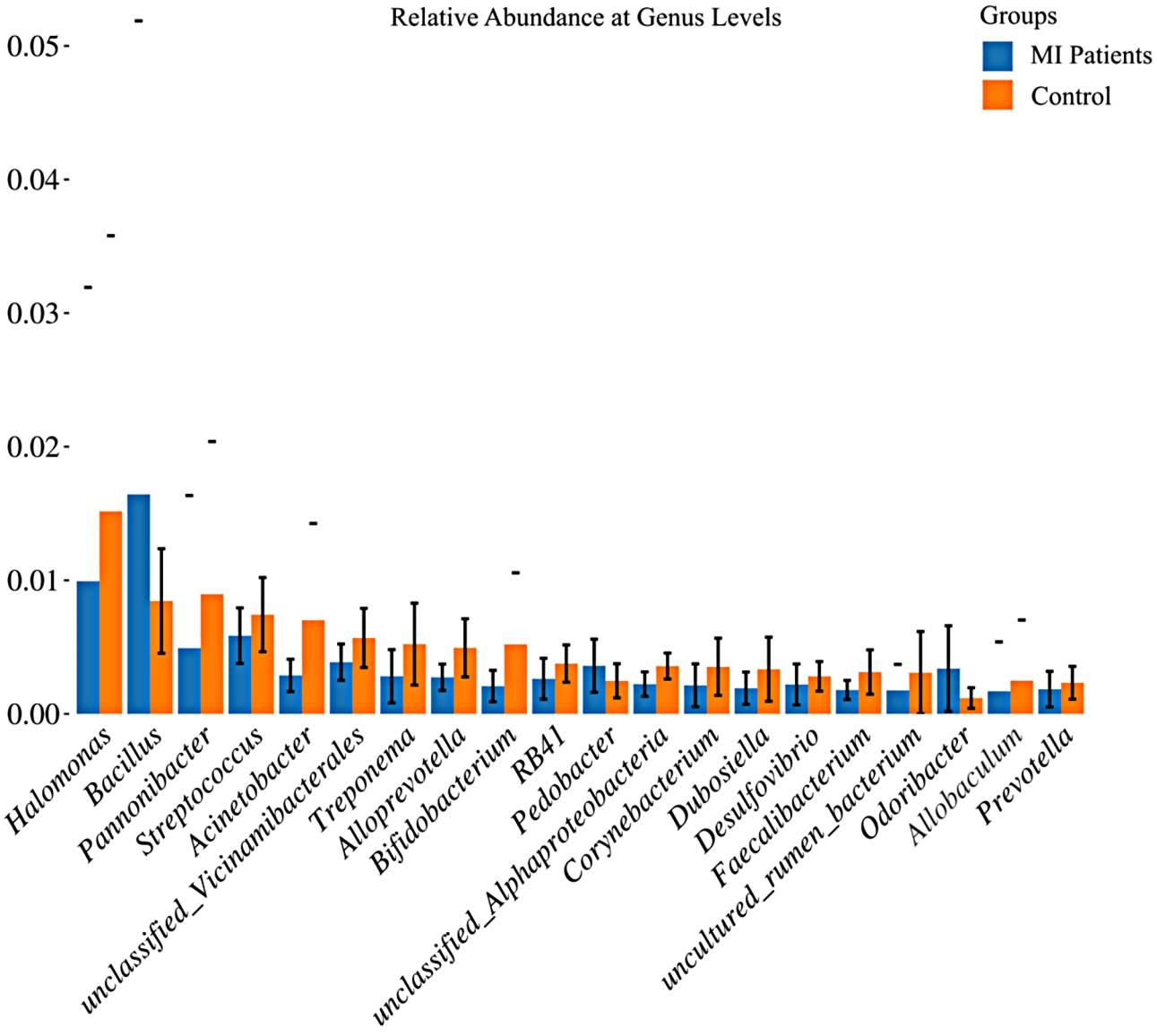

Fig. 5 The Wilcoxon rank-sum test was used to identify significant differences in blood microbial taxa between MI and control groups. Boxplots illustrate these differences at the bacterial genus level in both groups

Actinomyces, *Peptostreptococcus*, *Oribacterium*, *Parvimonas*, *Campylobacter*, *Lachnoanaerobaculum*, *Eubacterium _nodatum_group*, *Catonella*, *Stomatobaculum*, *Candidatus_Saccharimonas*, and *Peptococcus* were significantly enriched in healthy group ($p < 0.05$; Fig. 9).

Distinct bacterial taxa across three distinct compartments between both groups

One of the key study objectives was to identify shared and distinct microbiota across the blood, gut, and oral compartments. Six significantly distinct bacterial taxa Proteobacteria, Verrucomicrobiota, Alphaproteobacteria, Pseudomonadales, Rhizobiales, and Lactobacillaceae were identified in the healthy group. Additionally, unclassified_Lachnospiraceae genus and unclassified_Lachnospiraceae species were observed in the blood of MI patients.

Following the blood microbiota analysis, the healthy group exhibited distinct bacterial taxa, including Clostridia, Lachnospirales, Bifidobacteriales, Bifidobacteriaceae, Lachnospiraceae, Tannerellaceae, *Faecalibacterium*, *Blautia*, *Bifidobacterium*, and *Romboutsia*. In contrast, the MI group showed significant enrichment of Enterobacterales, Selenomonadaceae, and *Dialister* in fecal samples.

The oral microbiota analysis revealed that the healthy group had significant enrichment in Fusobacteriota, Fusobacteriia, Negativicutes, Saccharimonadia, Fusobacteriales, Veillonellales, Selenomonadales, Actinomycetales, Peptostreptococcales, Tissierellales,

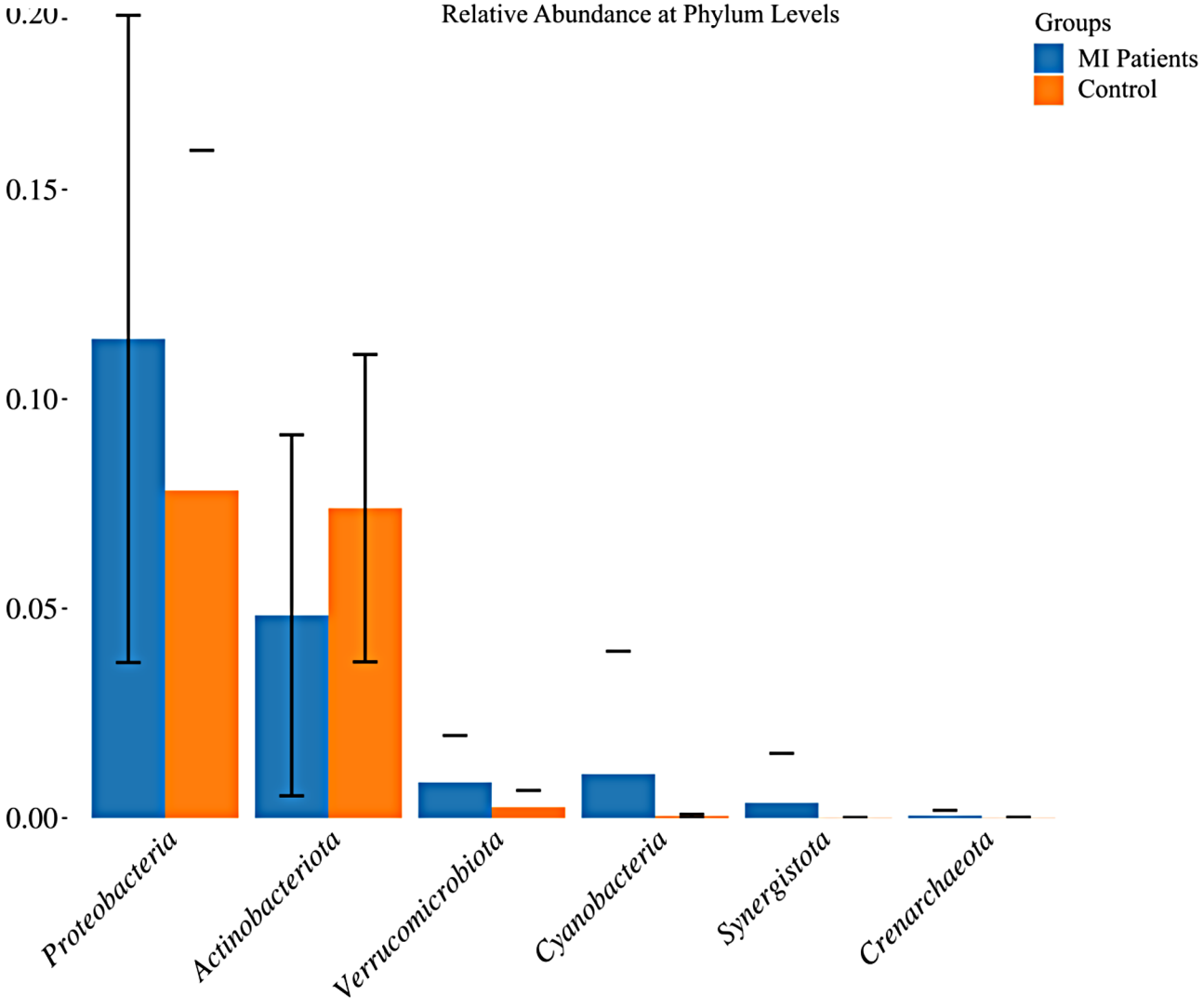

Fig. 6 The Wilcoxon rank-sum test identified significant differences in gut microbial taxa between MI and control groups, as shown in boxplots depicting variations at the bacterial phylum level

Saccharimonadales, Veillonellaceae, Porphyromonadaceae, Fusobacteriaceae, Leptotrichiaceae, Actinomycetaceae, Saccharimonadaceae, *Veillonella*, *Porphyromonas*, *Fusobacterium*, *Leptotrichia*, and *Actinomyces*. In contrast, the MI group showed significant enrichment of Actinobacteriota, Bacilli, Actinobacteria, Gammaproteobacteria, Lactobacillales, Micrococcales, Streptococcaceae, Micrococcaceae, Carnobacteriaceae, *Streptococcus*, *Rothia*, and *Granulicatella* (Fig. 10). These findings highlight key microbial taxa associated with health and disease states, providing a potential basis for diagnostic and therapeutic strategies targeting specific microbiota. Further studies are recommended to explore the functional implications and causal relationships of these microbial shifts.

Co-occurrence network of blood, gut, and oral microbiotas at phylum and genus levels

We conducted a detailed correlation analysis to explore the relationships between relatively abundant phyla, their corresponding genera, and their associations with other phyla and genera across blood, gut, and oral microbiota in patients with MI and the control group. This analysis aimed to uncover potential interactions and patterns of co-occurrence or exclusion that may contribute to the distinct microbial profiles observed in MI. Our findings revealed 15 genera within the phylum Firmicutes that exhibited significant associations with various other genera. Notably, *Subdoligranulum* and *Faecalibacterium* were negatively correlated with *Prevotella_7* and *Neisseria*, while *Blautia* displayed negative correlations with multiple genera, including *Prevotella_7*, *Prevotella*, *Porphyromonas*, *Neisseria*, *Leptotrichia*, and *Rothia*.

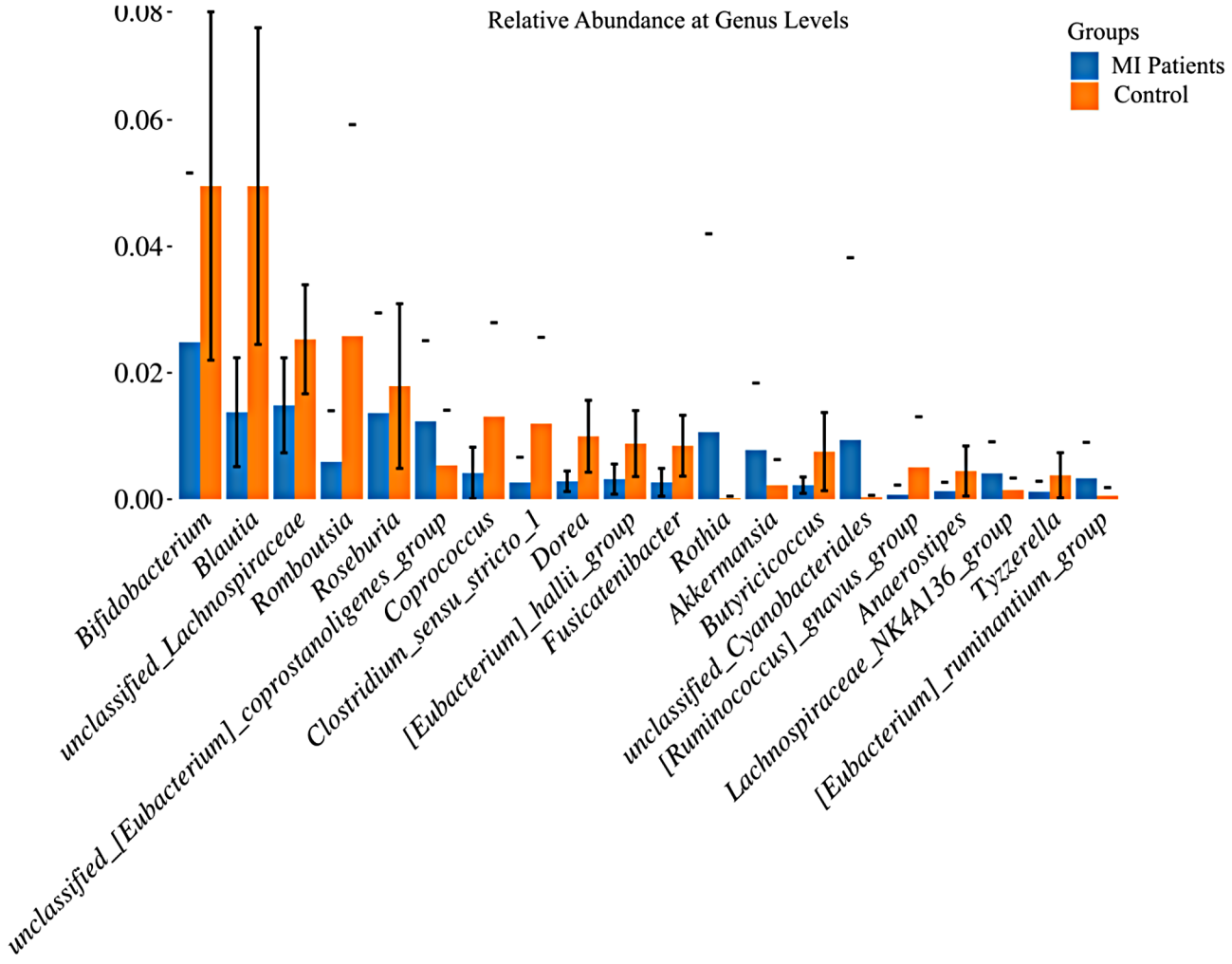

Fig. 7 The Wilcoxon rank-sum test identified significant differences in gut microbial taxa between MI and control groups, as shown in boxplots depicting variations at the bacterial genus level

Conversely, *Lachnoclostridium* exhibited negative correlations with *Prevotella_7* but positive associations with other genera from different phyla. These findings suggest that several Firmicutes genera have negative correlations with phyla Bacteroidota and Proteobacteria.

Additionally, seven genera from the phylum Bacteroidota, including *Parabacteroides*, *Alistipes*, *Prevotella_7*, and *Bacteroides*, demonstrated distinct associations. For example, *Prevotella_7* showed negative correlations with *Blautia*, *Parabacteroides*, *Subdoligranulum*, *Faecalibacterium*, and *Bifidobacterium* while positively correlating with *Prevotella*, *Porphyromonas*, *Neisseria*, and *Leptotrichia*. Three genera from the phylum Proteobacteria-*Halomonas*, *Neisseria*, and *Haemophilus* were also identified, with *Neisseria* showing negative correlations with *Blautia*, *Subdoligranulum*, and *Faecalibacterium* while being positively associated with *Prevotella_7*, *Leptotrichia*, and *Haemophilus*.

Furthermore, three genera from Actinobacteria - *Actinomyces*, *Rothia*, *and Bifidobacterium* displayed distinctive correlations. *Actinomyces* showed positive associations with *Veillonella*, *Granulicatella*, and *Defluviitoga*, while *Rothia* was negatively correlated with *Parabacteroides* and *Blautia* but positively associated with *Streptococcus*, *Granulicatella*, and *Leptotrichia*. Lastly, *Bifidobacterium* demonstrated negative correlations with *Prevotella_7* and positive associations with *Subdoligranulum* and *Streptococcus*. These complex interactions, detailed in Fig. 11, provide critical insights into the intricate microbial interplay across biological niches, underscoring the potential roles of specific microbial relationships in the context of MI.

Association between blood, gut, and oral microbiotas and clinical markers

Using the Spearman correlation test, we further assessed the correlation between the distinct bacterial species

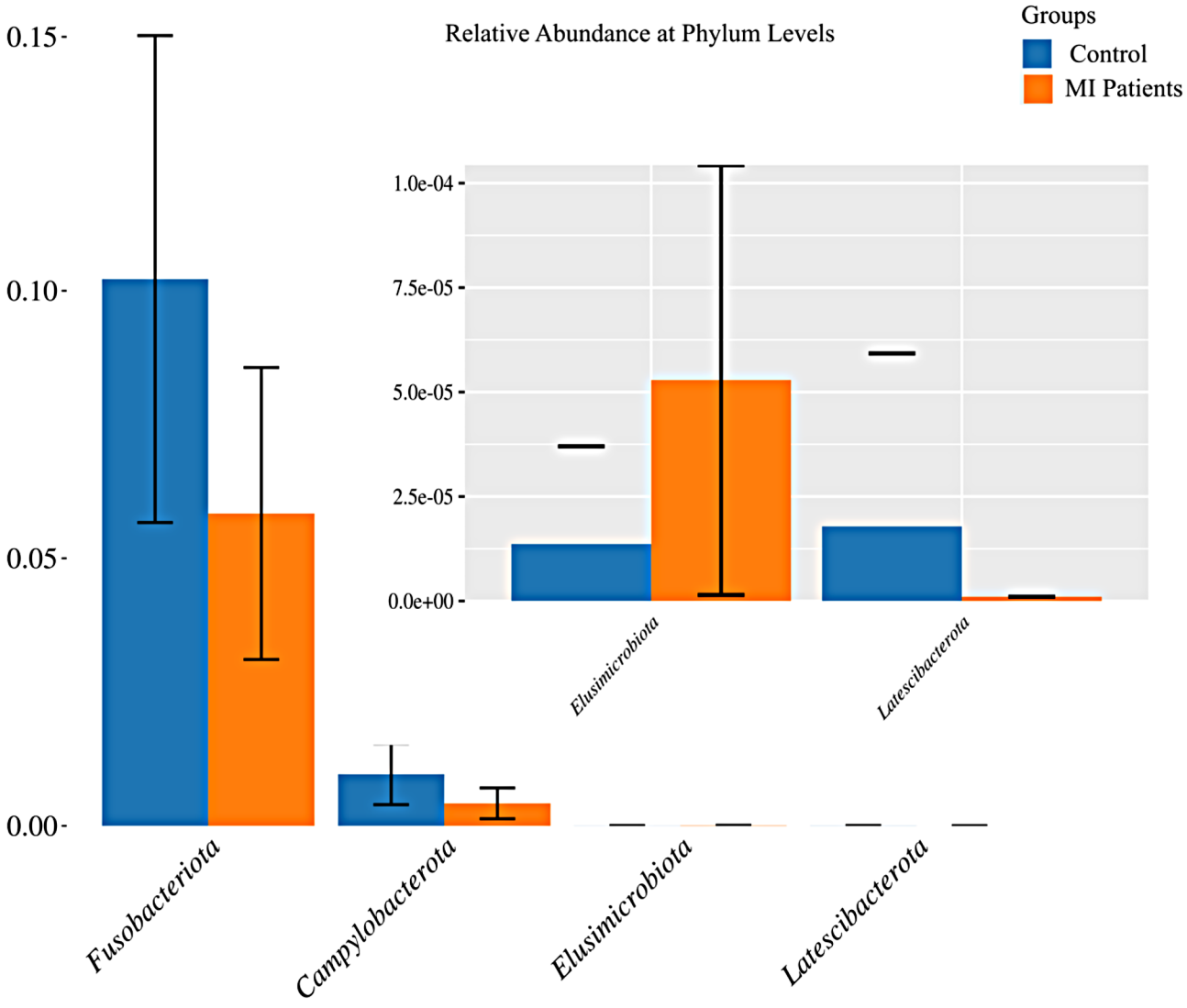

Fig. 8 The Wilcoxon rank-sum test detected significant differences in oral microbial taxa between MI and control groups, with boxplots showing significant variations at the bacterial phylum level

with clinical markers. Our findings reveal a significant negative correlation between the phylum Verrucomicrobiota and Hb and PLT. At the same time, the order Rhizobiales exhibits a significant positive correlation with PLT (Fig. 12A). Likewise, we assessed the correlation between gut microbiota and disease markers. The *Clostridia* class exhibits a significant positive correlation with PLT levels and a negative correlation with CRP. Lachnospirales, Lachnospiraceae, and *Blautia* demonstrate significant negative correlations with neutrophils and CRP. Enterobacterales, Bifidobacteriales, and Bifidobacteriaceae correlate positively with LDL, whereas *Selenomonadaceae* correlate negatively with PLT (Fig. 12B).

Furthermore, the oral genus *Actinomyces* was positively correlated with TG and Hb. *Streptococcus* was positively correlated with HDL. *Leptotrichia* was positively correlated with TC, LDL, neutrophil, and CRP. *Veillonella* was positively correlated with LDL, and phylum Fusobacteriota was positively correlated with LDL and CRP (Fig. 12C).

Functional prediction of blood, gut, and oral microbiota

The phylogenetic investigation of communities by the reconstruction of unobserved states (PICRUSt2) method was used to predict the functional profiles of the blood microbiota based on KEGG pathways. Among the top 10, predicted functional pathways of the blood microbiome between the control and MI groups were carbohydrate metabolism, lipid metabolism, metabolism of cofactors and vitamins, energy metabolism, amino acid metabolism, nucleotide metabolism, biosynthesis of other secondary metabolites, metabolism of terpenoids and polyketides, xenobiotics biodegradation and metabolism, and metabolism of other amino acids. However,

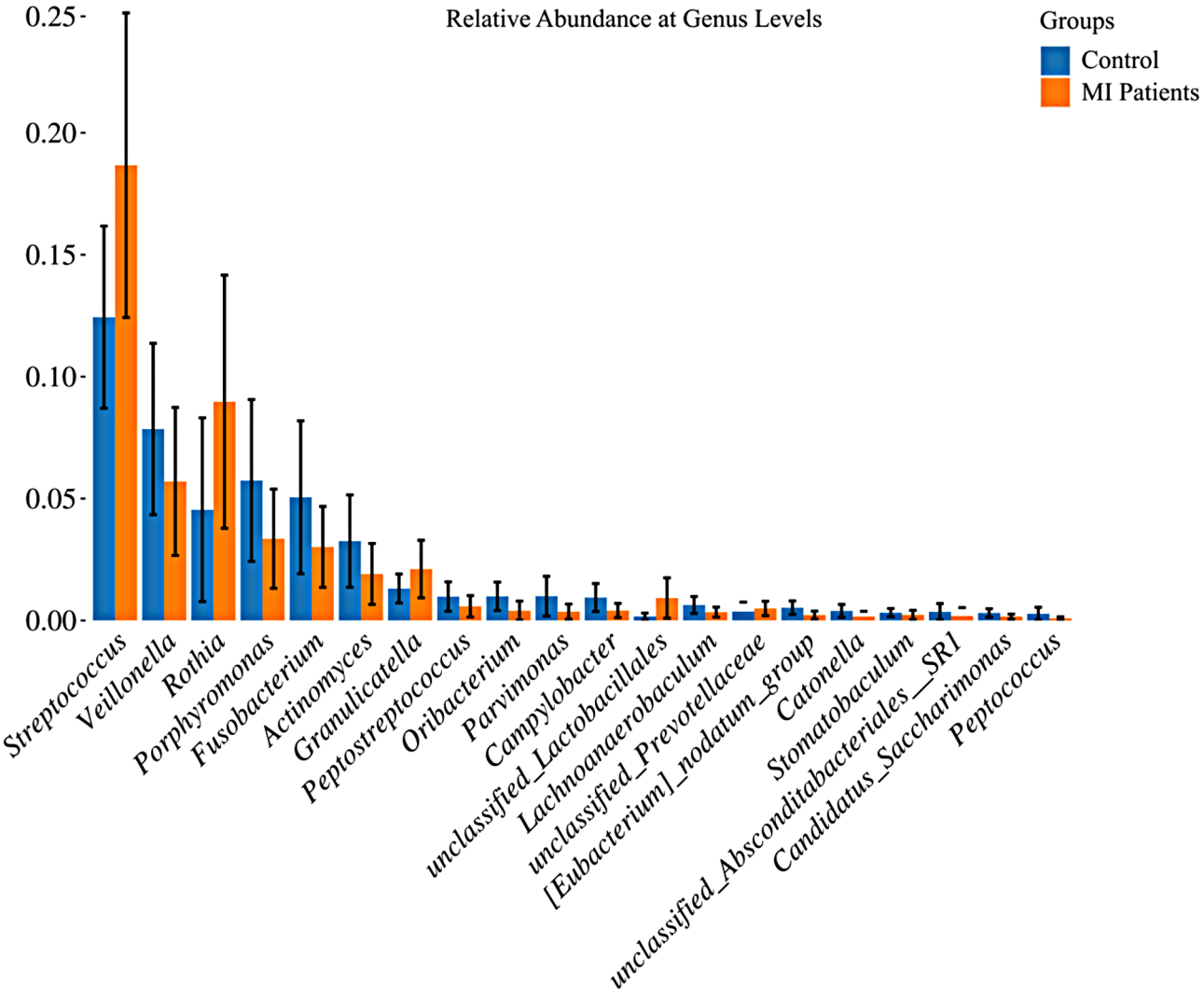

Fig. 9 The Wilcoxon rank-sum test detected significant differences in oral microbial taxa between MI and control groups, with boxplots showing significant variations at the bacterial genus level

no statistically significant differences were observed in the blood functional pathways between the two groups (Table 1). Similarly, no significant differences were identified in the functional prediction pathways of gut and oral microbiota between the healthy and MI groups (Supplementary Table S3).

Discussion

Numerous diverse microbial species reside in various human body tissues, including the skin, oral mucosa, and gastrointestinal tract. Imbalances in the microbiota are associated with multiple human diseases that affect regions beyond the local anatomic site, such as neurologic and cardiovascular disorders [40]. Efforts have been made to define microbial components of the human genetic and metabolic landscape to better understand the underlying pathophysiology and develop novel therapeutic strategies [6]. The current study comprehensively analyzed the blood, gut, and oral microbiomes of MI patients relative to those of sex-matched healthy controls. Our findings revealed significant differences in the composition of the blood, gut, and oral microbiome between the two groups. Our findings also revealed a significant correlation between key taxa and clinical markers for MI.

The present findings showed lower alpha diversity in the blood, gut, and oral microbiome in the MI group than in the controls. The blood samples exhibited the highest number of OTUs compared to fecal and saliva samples, suggesting a potential influx of more bacteria into the bloodstream. Ordinarily, the mucous membrane lining the mouth and digestive tract acts as a barrier, which helps prevent bacteria from entering the bloodstream. However, inflammation in these regions can lead to increased permeability, enabling bacterial translocation [41, 42]. Mounting evidence strongly supports the significant correlation between gut and oral microbiota

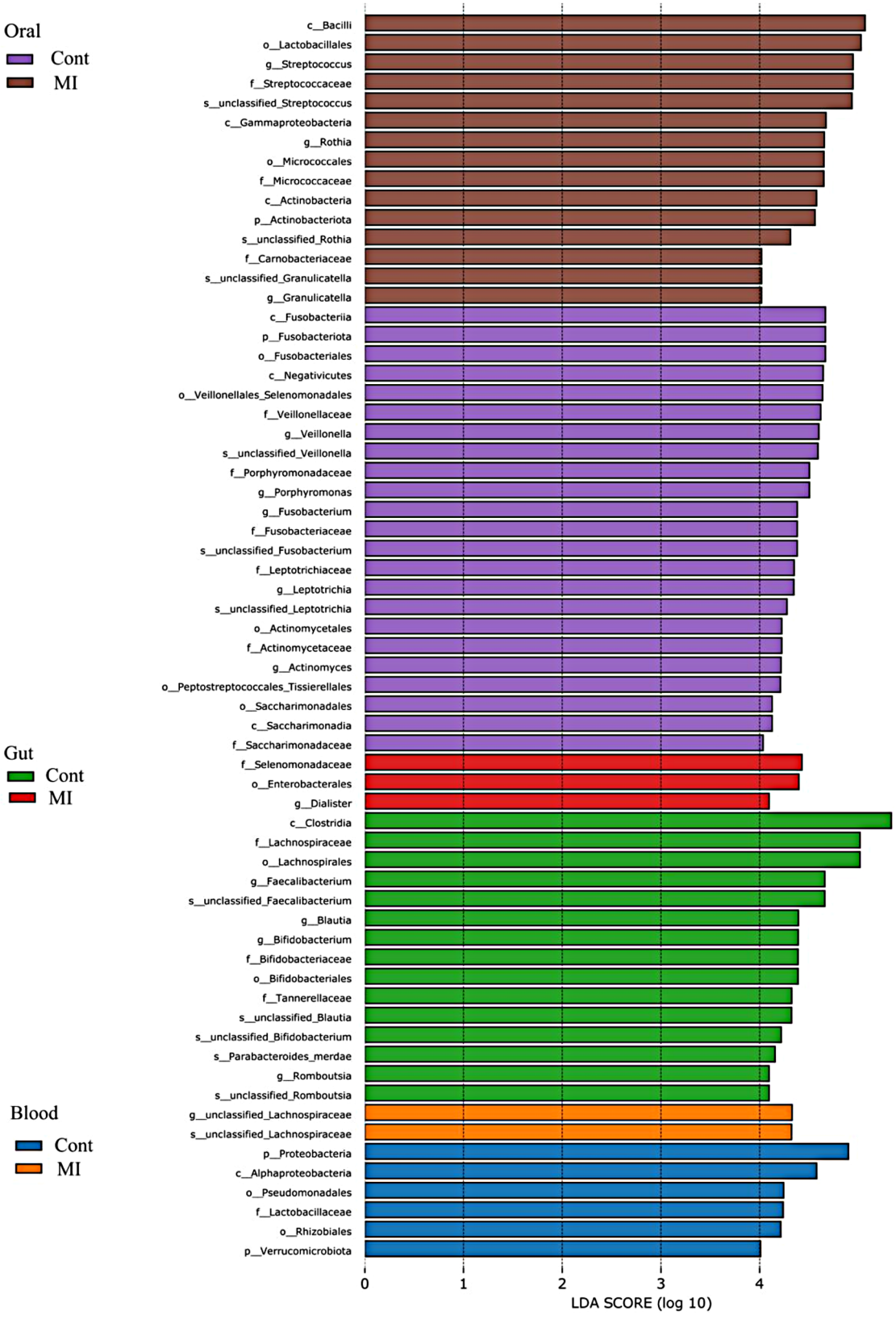

Fig. 10 Linear Discriminant Analysis (LDA) Effect Size (LEfSe) analysis was conducted on microbial taxa from blood, gut, and oral samples obtained from the study subjects. (A) LDA scores revealed a distinctive representation of microbial taxa in the blood, gut, and oral between healthy and patient groups

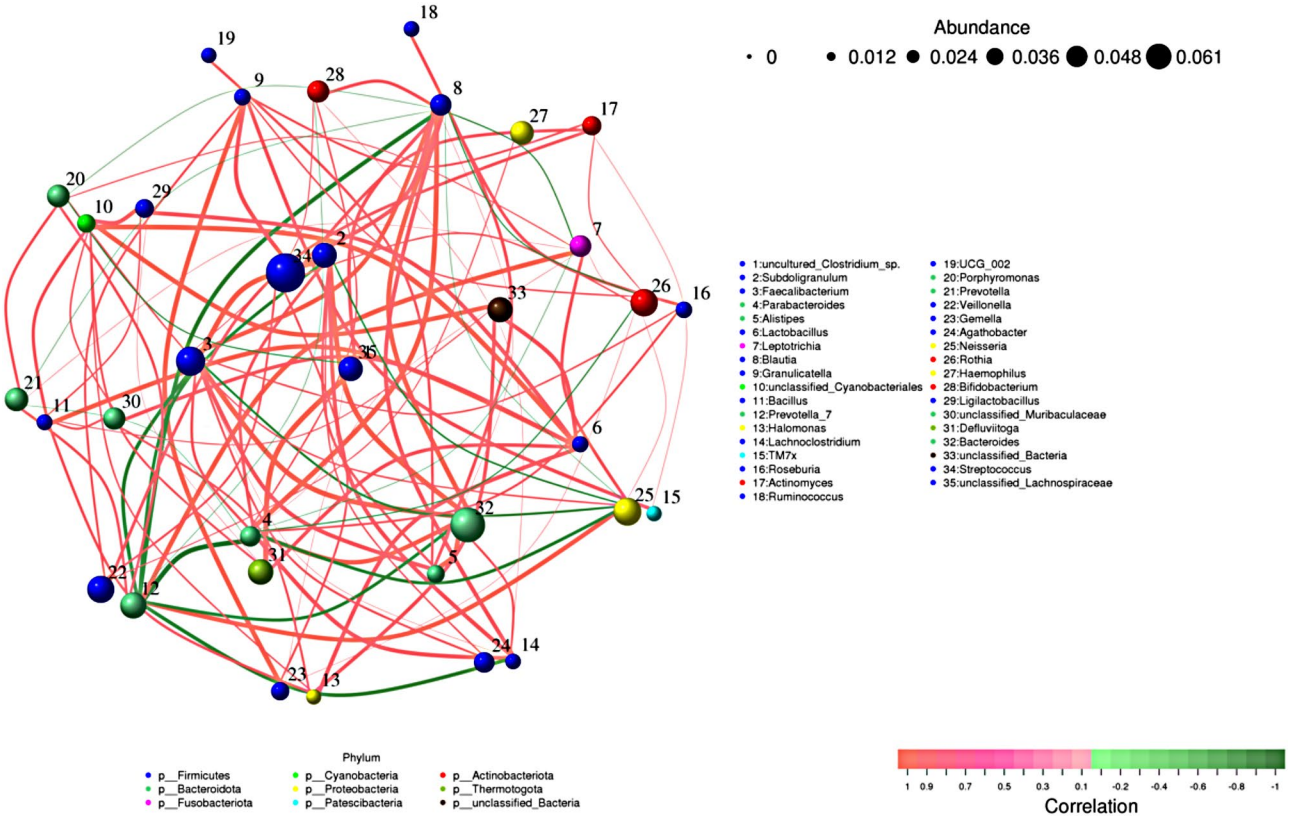

Fig. 11 The association between blood, gut, and oral microbiota at phyla and genera levels. The nodes represent bacterial species, and the edges (the lines connecting the nodes) represent the strength and type of correlation between these species. The node size likely corresponds to the abundance of the species, and the edge thickness indicates the strength of the correlation

dysbiosis and the onset of CVD [43, 44]. Periodontitis and other oral diseases have the potential to facilitate the migration of oral microbiota into the bloodstream. This process can potentially trigger conditions such as endocarditis and MI [10, 45], and they may play a potential role in the progression of atherosclerosis. Our analysis unveiled numerous shared OTUs between the blood and the gut, indicating that bacteria detected in the blood may indeed originate from both the distal gut and the oral cavity. One potential mechanism for this dissemination of bacteria into the bloodstream could involve epithelial linings, such as from gut injury or barrier dysfunction, or oral infections like tooth infections [19]. Thus, blood pathobiology may mimic the gut and oral environments, suggesting a key role for select microbes in disease progression.

Until recently, the blood microbiome has received scant attention, as systemic circulation was traditionally believed to be sterile, with circulating bacteria mainly associated with sepsis cases. However, bacterial DNA has been detectable in blood samples, albeit at low levels [10, 46–48]. Koren et al. detected the blood microbiome in both patients with MI and controls, which demonstrated the presence of phyla *Firmicutes*, *Bacteroidota*, and *Proteobacteria*, along with genera *Streptococcus*, *Bacteroides*, and *Faecalibacterium* likely originating from the gut microbiota. The substantial bacterial richness prompted us to delve deeper into the bacteria's origin. Intriguingly, bacteria enriched in patients with MI predominantly originated from the gut. For instance, *Bacteroides*, previously detected in gut samples, exhibited the highest abundance in patients with MI [10]. This suggests that the gut microbiota could be a pivotal factor contributing to the heightened microbial richness and diversity observed in patients with MI. Prior research has established a correlation between diverse infectious agents and MI [35–38] For instance, Amar et al. identified a small subset of recognized cholesterol-degrading bacterial families and genera [49], including *Nocardiacae*, *Aerococcaceae*, *Gordonia*, *Propionibacterium*, *Chryseobacterium*, and *Rhodococcus*, present in the blood samples of both controls and patients with MI. Interestingly, they observed a decrease in the relative abundance of all these bacterial species in the blood of patients with MI [35]. In contrast, a recent study found significantly higher levels of *Actinobacteria* in patients with MI, along with the genus *Bifidobacterium* and family *Bifidobacteriaceae*, respectively [36], these findings suggested that blood

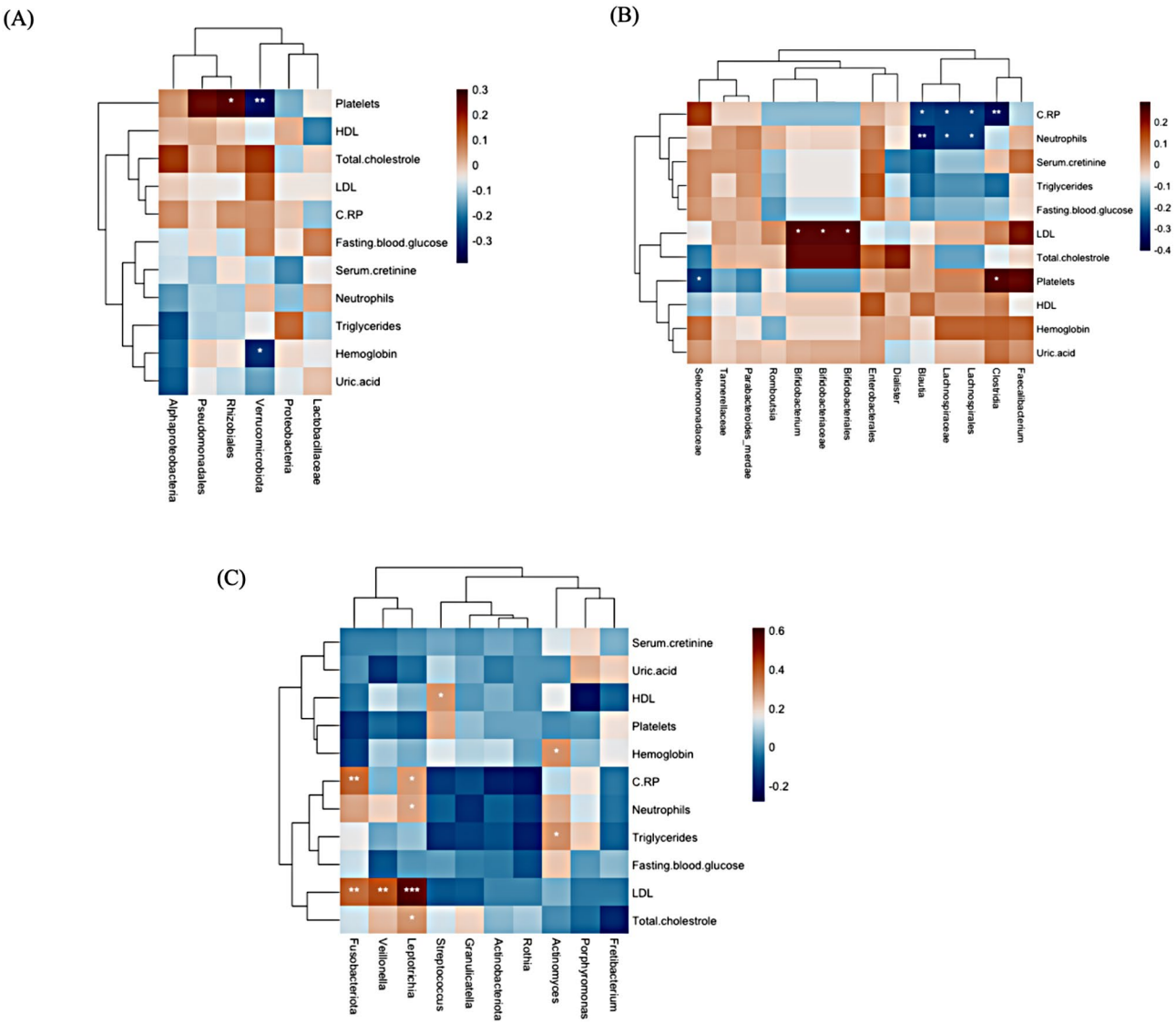

Fig. 12 The correlation between distinct blood, gut, and oral microbiota with MI clinical markers. (**A**) shows the correlation heatmap between distinct blood microbiota and disease markers. (**B**) Display the correlation heatmap between gut microbiota and disease markers. (**C**) Depicts the correlation heatmap between distinct oral microbiota and clinical markers for MI. Significance levels are indicated as ***$p < 0.001$, **$p = 0.001$, *$p = 0.01$

microbiome shifts as potential diagnostic markers for MI progression. Another study showed that individuals with acute coronary syndrome had elevated *Proteobacteria* and *Acidobacteria*, while those with chronic disease had enriched *Firmicutes* and *Lactobacillus* [37]. Most recently, Chen et al. identified varied blood microbial profiles in acute MI and unstable angina patients. *Firmicutes* and *Bacteroidota* were elevated in MI, while *Proteobacteria* and *Ralstonia* were more common in unstable angina [33]. Qian et al. observed a reduction in *Proteobacteria* levels in the gut of patients with MI within a Chinese cohort [50]. Bijla et al. reported a decline in *Firmicutes* levels in CVD cases linked to tobacco use and dietary factors [51]. Similarly, a couple of studies reported a decreased abundance of *Firmicutes* in the gut of Patients with MI [52–54]. In contrast, our study found elevated levels of *Proteobacteria* and *Firmicutes* in patients with MI compared to healthy individuals, while no association was observed between *Firmicutes* and MI clinical indicators. Moreover, inconsistencies in the genera and species reported across studies suggest that the microbial composition is more complex than previously documented [36, 37]. This underscores the need for more comprehensive investigations to fully understand the microbial community's role in these conditions. Moreover, the patients with MI were older than the healthy individuals, suggesting that age may influence microbiome composition and contribute to disease development. Lee et al. reported a significant increase in the abundance of Gammaproteobacteria in individuals over sixty years of age, while the

Table 1 Blood microbiome-based functional prediction pathways between healthy and MI groups

Metabolic pathways	Healthy	Patients	*P*-value
Carbohydrate metabolism	9.29 ± 0.24	9.34 ± 0.21	0.76
Lipid metabolism	2.16 ± 0.05	2.15 ± 0.14	0.94
Metabolism of cofactors and vitamins	4.06 ± 0.04	4.04 ± 0.06	0.77
Energy metabolism	4.28 ± 0.09	4.30 ± 0.25	0.90
Amino acid metabolism	6.99 ± 0.23	7.02 ± 0.24	0.89
Nucleotide metabolism	3.44 ± 0.13	3.43 ± 0.13	0.91
Biosynthesis of other secondary metabolites	0.89 ± 0.04	0.91 ± 0.05	0.77
Metabolism of terpenoids and polyketides	1.13 ± 0.02	1.12 ± 0.03	1.13
Xenobiotics biodegradation and metabolism	1.44 ± 0.17	1.39 ± 0.17	0.79
Metabolism of other amino acids	1.52 ± 0.04	1.49 ± 0.08	2.22

relative abundances of Alphaproteobacteria, Deltaproteobacteria, and Clostridia were significantly reduced ($P = 0.0001$) [55]. These microbial composition shifts suggest age-related microbiome changes, potentially impacting health outcomes. However, our study presents contrasting findings, highlighting adverse results. Further research is needed to determine whether these microbial changes result from aging or are specifically associated with MI, as the observed variations may reflect complex interactions between age, disease state, and microbiota.

Despite these significant findings, certain studies indicate that bacteria detected in the bloodstream may derive specifically from the oral cavity and gut environments [6, 10, 19, 23]. These findings imply that microbial shift may contribute to MI, characterized by heightened levels of *Proteobacteria* and *Enterobacteriaceae* in patients with MI, which diverge from their typical proportions in the gut microbiota. Likewise, a prior study indicates that an elevated presence of *Proteobacteria*, often observed in individuals with metabolic disorders, serves as an indicator of gut dysbiosis [56]. Jie et al. observed higher levels of *Enterobacteriaceae* in individuals diagnosed with atherosclerosis compared to those in control subjects [57]. The decrease in the abundance of short-chain fatty acid (SCFA)-producing bacteria and the rise in the prevalence of lipopolysaccharide (LPS)-producing bacteria are consistent with findings reported previously [58–60]. *Bacteroides*, a probiotic typically residing in the human gut, can become pathogenic upon migration to other body sites, potentially causing infections in the oral cavity, nervous system, and bloodstream [61]. The current findings unveiled a higher abundance of *Bacteroides* in both the MI and healthy groups, with a particularly pronounced enrichment noted in the MI group. It's widely acknowledged that inflammation plays a significant role in atherosclerosis development, and *Bacteroides* might contribute to MI by triggering inflammatory responses in the body. *Blautia*, an anaerobic bacterium commonly found in the human gut, has attracted significant attention from researchers because of its ability to alleviate inflammatory responses and its role in regulating fat metabolism [62]. In a cohort study conducted in Japan, a negative correlation was found between the presence of *Blautia* in the gut and the occurrence of obesity and type 2 diabetes. Administering a specific dosage of *Blautia* orally to mice resulted in an amelioration of symptoms associated with obesity and diabetes [63]. Yet, there is a scarcity of research on the distribution of *Blautia* beyond the gut and its related functions. Our findings suggest that *Blautia* is present in the blood of both healthy and those with MI, with a higher abundance seen in the healthy group. Further investigation is required to clarify the ectopic distribution of *Blautia* and its potential implications in CVD.

Furthermore, the current findings highlight that the oral microbial profiles show significant differences between control and MI groups due to direct environmental exposure, rapid changes, and a strong link to systemic inflammation and atherosclerosis. Unlike the gut or blood microbiota, the oral microbiome is more dynamic and directly influences cardiovascular health. Our study identified a distinct abundance of genera *Streptococcus* and *Rothia*, as well as families *Streptococcaceae* and *Micrococcaceae*, in patients with MI, while the healthy group showed a unique prevalence of phylum *Fusobacteriota* and family *Lachnospiraceae*. Koren et al. examined bacterial diversity in atherosclerotic plaques, oral, and stool samples collected from individuals undergoing carotid endarterectomy. They identified resemblances in the microbiota composition between the patients with MI and the healthy [8]. Our study identified a notable disparity in the oral microbiome between patients with MI and healthy groups. Another study investigated ST-Segment Elevation Myocardial Infarction (STEMI) patients during the active phase who had acquired coronary thrombus [6]. STEMI occurs due to plaque rupture, marking a distinct event in the prolonged progression of atherosclerosis, which can span years or even decades. Variations in study designs led to notable disparities in the findings [6]. These findings indicate that patients with MI harbor intricate and specialized microbial communities. Moreover, alterations in the composition of the oral microbiome could potentially serve as a diagnostic biomarker for monitoring the progression of MI. However, our findings suggested that elevated levels of *Streptococcus* and *Rothia* species in saliva serve as a risk factor for MI. This phenomenon might stem from the displacement of oral microbiota, leading to an imbalance in the immune system and inducing inflammation, thereby facilitating the formation of atherosclerosis.

However, this proposition remains speculative, and the precise mechanism requires further investigation.

Spearman's rank correlation coefficient analysis showed a notable negative correlation between certain blood microbiota, like V*errucomicrobiota*, and hemoglobin levels within the healthy group. Conversely, *Rhizobiales* exhibited a positive correlation with PLT counts (Table S1). Further research is warranted to validate these findings. Similarly, distinct gut microbiota, such as *Clostridia* and *Enterobacterales*, exhibited a positive correlation with PLT and LDL. Conversely, *Lachnospirales*, *Lachnospiraceae*, and *Blautia* demonstrated a negative correlation with CRP and neutrophil levels. Additionally, *Selenomonadacea* displayed a negative correlation with PLT counts in patients. Subsequently, the distinct oral microbiota, including *Granulicatella* and *Carnobacteriaceae*, showed a significant positive correlation with neutrophil counts and UA levels, while exhibiting a negative correlation with TC. Moreover, *Fusobacteriota*, *Fusobacteriia*, and *Fusobacteriales* displayed a negative correlation with neutrophil counts. However, this result has not previously been described. Further, longitudinal studies need to elucidate temporal changes in microbiome profiles and their associations with cardiovascular health. Additionally, investigating the mechanistic underpinnings of these correlations may unveil novel therapeutic targets for MI management. Integrating multi-omics approaches could provide a comprehensive understanding of the complex interplay between microbiota and host physiology in CVD.

Limitations of the study

Our results provided the possibility to discover new biomarkers for the prediction of MI using microbiota. However, there is still room for further exploration in this study: (i) The sample size in this study is relatively small, which may reduce the statistical power to detect subtle differences in microbiome profiles, potentially increasing the risk of false negatives. Additionally, the limited representation of inter-individual variability could lead to spurious correlations: (ii) Age, a key factor influencing both CVD and microbiome composition, was not fully accounted for in this study but should be integrated into future analyses to enhance the robustness of potential conclusions: (iii) The cross-sectional design limits the ability to determine whether the observed changes in microbial taxa play a causal role in MI pathogenesis or arise as a secondary consequence of disease processes. Longitudinal studies are needed to clarify these relationships: (iv) Dietary habits can influence microbial profiles, while lifestyle factors such as smoking and exercise may shape microbial composition, potentially introducing biases in the observed associations: (v) Integrating multi-omics approaches, such as metagenomics, metabolomics, and transcriptomics, would provide a more comprehensive characterization of microbial functional pathways and their metabolic outputs, helping to bridge existing gaps in understanding microbial contributions to MI pathophysiology: (vi) Future studies should leverage multicenter collaborations to recruit geographically and ethnically diverse populations, enhancing statistical power and better capturing inter-individual variability.

Conclusion

Our findings revealed significantly distinct microbial composition across blood, gut, and oral microenvironments between MI and healthy groups, highlighting a unique microbial signature associated with MI. These results reinforce prior evidence suggesting that microbial dysbiosis in the blood may actively influence MI progression [31, 32]. We hypothesize that the distinct abundance of phylum Thermotogota, Acidobacteria, Cyanobacteria, and genus *Defluviitoga* in the blood suggests that these bacterial taxa are indigenous to the bloodstream and may play a potential role in human physiology. Additionally, the distinct presence of *Faecalibacterium* in the gut and Fusobacteriota, Patescibacteria, and genera such as *Neisseria*, *Rothia*, *Veillonella*, and *Prevotella_7* in the oral cavity highlights the compartmentalized nature of microbiomes, further emphasizing their potential impact on host health. However, as this observational study was conducted within a Chinese population, generalizing the findings regarding the relationship between the blood microbiome and health or disease in other populations remains challenging. Furthermore, intriguing correlations between microbial profiles in blood, gut, and oral compartments and key disease biomarkers, specifically LDL, Hb, and PLT, point to specific bacteria with potential predictive and mechanistic roles in MI pathology. To validate these findings, future studies should include larger sample sizes, multicenter collaborations, diverse ethnic populations, and advanced metagenomic and metabolic analyses.

Abbreviations

BH	Blood of Healthy individuals
BP	Blood of MI patients
BMI	Body mass index
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
FDR	False discovery rate
FBG	Fasting blood glucose
FH	Fecal sample of healthy individuals
FP	Fecal sample of MI patients
Hb	Hemoglobin
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MI	Myocardial infarction
mmHg	Millimeters of mercury Hg
NEUT	Neutrophil
PCR	Polymerase chain reaction

PLT	Platelet
RBC	Red blood cell
SBP	Systolic blood pressure
Scr	Serum creatinine
SH	Saliva sample of healthy individuals
SP	Saliva sample of MI patients
TC	Total cholesterol
TG	Triglycerides
UA	Uric acid
WBC	White blood cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12866-025-03878-9.

Supplementary Material 1

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Author contributions
IK made this study design, analyzed and explained the data, and then drafted this manuscript. PX and YX did subject recruitment, provided samples, and subjects clinical data. IK, SL, and TS were responsible for data acquisition, analysis, and interpretation work. ZL and XX supervised the study, checked the design of this study, and revised the manuscript. All authors were responsible for the authenticity of the data and went over and approved the final manuscript.

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Data availability
The raw data analyzed in this study has been deposited in the National Center for Biotechnology Information with the primary accession code blood "PRJNA1174175", oral "PRJNA1174709" and gut "PRJNA1174683.

Declarations

Ethics approval and consent to participate
Clinical investigations were performed according to the Declaration of Helsinki. The present study was reviewed and approved (Approval #: *Lzujcyxy-20240342*) by the review boards at Lanzhou University. All enrolled patients and volunteers provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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