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Basic Study

Mucosal bacterial dysbiosis in patients with nodular lymphoid hyperplasia in the terminal ileum

Qiao-Li Jiang, You Lu, Meng-Jie Zhang, Zhen-Yu Cui, Zhong-Mei Pei, Wen-Hua Li, Lun-Gen Lu, Jing-Jing Wang, Ying-Ying Lu

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Abstract**BACKGROUND**

Nodular lymphoid hyperplasia (NLH) in the small intestine is a rare benign lesion characterized by multiple small nodules on the intestinal surface. Patients with terminal ileal NLH may experience long-term abdominal pain, diarrhea, and abdominal distension, among other symptoms. Supplementation with probiotics could mitigate these symptoms. NLH is linked to the immune system, and it may result from accumulation of plasma-cell precursors due to a maturational defect during the development of B lymphocytes. The intestinal microbiome plays an essential role in the immune system. Thus, we speculate that the gut flora plays a key role in terminal ileal NLH.

AIM

To explore the correlation between intestinal flora and terminal ileal NLH.

METHODS

We collected mucosal biopsy samples that were obtained *via* colonoscopy from 15 patients with terminal ileal NLH (the test group) and 15 normal subjects (the control group). We subsequently performed 16S-rRNA gene amplicon sequencing of these samples, and the results were evaluated using alpha diversity, beta diversity and microbial composition analyses. The Phylogenetic Investigation of Communities by Reconstruction of Unobserved States was used to predict the

metabolic pathways and orthologous groups according to the Kyoto Encyclopedia of Genes and Genomes database.

RESULTS

Compared with the control group, the terminal ileal NLH group showed an increased alpha diversity ($P < 0.05$). The overall intestinal microbiota in the NLH group was significantly different from that of the control group ($P < 0.05$), implying that there was the dysbiosis in the terminal ileal NLH patients. The relative abundance of phylum Bacteroidetes was significantly lower in the NLH group, while that of Patescibacteria and Campilobacterota was significantly higher. The genus *Bacteroides* was the dominant gut microbiota in both groups, but its abundance was significantly lower in the test group than it was in the control group. Conversely, the relative abundances of *Haemophilus*, *Streptococcus*, *Pseudomonas*, *Actinomyces*, TM7X, *Fusobacterium nucleatum*, *Parvoimonas*, *Granulicatella*, *Helicobacter*, and the [*Eubacterium*] *nodatum* group were significantly higher in the test group than they were in the control group. In addition, several altered metabolic pathways, orthologous groups, and modules were found. For example, the Peptidoglycan biosynthesis and Aminoacyl tRNA biosynthesis were both increased in the test group.

CONCLUSION

Maintaining the microbial balance and supplementing targeted protective bacteria could improve symptoms and potentially reduce the risk of lymphoma transformation in patients with terminal ileal NLH.

Key Words: Hyperplasia; Bacteroides; Small intestine; Microbiome; Helicobacter pylori; Colonoscopy

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Core Tip: Nodular lymphoid hyperplasia (NLH) in the small intestine is a rare benign lesion characterized by multiple small nodules on the surface of the intestine. To explore the correlation between the intestinal flora and terminal ileal NLH, we performed bacterial 16S rRNA gene sequencing of mucosal samples from patients with terminal ileal NLH. Our results reveal that specific microflora may act on the mucosa of the small intestine and cause terminal ileal NLH. Therefore, maintaining the balance of intestinal flora and supplementing targeted protective bacteria may improve terminal ileal NLH symptoms and potentially reduce the risk of lymphoma transformation.

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INTRODUCTION

Nodular lymphoid hyperplasia (NLH) in the small intestine is a rare benign lesion, and its incidence has not yet been determined. It is characterized by multiple small nodules on the surface of the intestine, which are found to be present in the lamina propria and superficial submucosa of the intestine[1]. The diagnosis of NLH is mainly based on endoscopic and histological examinations, markedly including the presence of hyperplastic lymphoid follicles and mitotically active germinal centers with well-defined lymphocytic mantles[2]. Terminal ileal NLH is a type of NLH, and patients with terminal ileal NLH demonstrate multiple symptoms that seriously reduce the individual's quality of life, such as chronic diarrhea, abdominal pain, hematochezia, anemia, hypoproteinemia, among other symptoms[3]. Patients with irritable bowel syndrome are more likely to accompany with NLH[4]. During the clinical diagnosis and treatment of patients with terminal ileal NLH, we found that probiotics could improve gastrointestinal symptoms.

NLH may be associated with a risk factor for intestinal lymphoma, as the resolution of gastrointestinal tract nodular lymphoid hyperplasia has been shown following chemotherapy for extraintestinal lymphoma[5]. However, the pathogenesis of NLH has not been fully elucidated yet. A frequently proposed hypothesis implicates an intestinal antigenic trigger, possibly infectious, that leads to the repetitive stimulation and eventual hyperplasia of the lymphoid follicles, which may originate

from proliferative plasma cell precursors related to a maturational defect during the development of B lymphocytes[6]. NLH has been reported in patients with human immunodeficiency virus, common variable immunodeficiency, Giardia lamblia infection, helicobacter pylori (*H.pylori*) infection, familial adenomatous polyposis, and Gardner's syndrome[7]. The intestinal microbiome plays an essential role in the immune system; gut microbiota that colonize the human intestinal tract form a mutual symbiotic relationship with the host and play a key role in regulating the host immune system and metabolism[8, 9]. Conventionally, alterations in the gut microbiota are closely related to inflammatory bowel disease, obesity, colonic adenoma, and colorectal cancer[10-13], but whether the gut flora plays a role in NLH is unclear.

In this study, we performed bacterial 16S rRNA gene amplicon sequencing of mucosal tissue samples to study the gut microflora dysbiosis that is associated with terminal ileal NLH to determine what alterations occur in microflora and explore the correlation between the intestinal microflora and terminal ileal NLH. Moreover, we used molecular bioinformatic technology to predict the metabolic pathways that are involved in terminal ileal NLH, which will provide the possibility for further targeted intervention therapy.

MATERIALS AND METHODS

Clinical trial design and sampling

A total of 30 patients who underwent a colonoscopy in the Digestive Endoscopy Center at Jiading Branch of Shanghai General Hospital (Shanghai, China) from January 2021 to April 2021 were recruited for this study. A total of 15 Patients with terminal ileal NLH (11 males and 4 females aged 24-44 years) were assigned to the test group, while 15 healthy volunteers (7 males and 8 females aged 30-44 years) were assigned to the control group after undergoing a routine physical examination. There were no statistically significant differences in the general data between the groups ($P > 0.05$). Among the 15 patients with terminal ileal NLH, the most common symptom was diarrhea, followed by abdominal pain and abdominal distension.

Endoscopic images were reviewed and confirmed by the endoscopic team. Terminal ileal NLH was diagnosed using endoscopy and histopathology (Figure 1). We confirmed that there was no history of antibiotic or probiotic administration within the previous two months for all the subjects. Patients with diabetes mellitus, inflammatory bowel disease, previous colon resection, colorectal cancer, or a body mass index ≥ 30 kg/m² were excluded. This research was approved by the research ethics boards of Shanghai General Hospital (2021KY085), and written informed consent was obtained from all the patients before sample collection. We collected mucosal biopsy samples that were obtained *via* colonoscopy from both groups. All samples were frozen immediately after sampling and stored at -80 °C.

DNA extraction/isolation

Microbial genomic DNA was extracted from each sample using the E.Z.N.A.[®] Stool DNA Kit (Omega Bio-tek, Inc., GA) according to the manufacturer's instructions. The samples were suspended in 790 μ l of sterile lysis buffer (4M guanidine thiocyanate; 10% N-lauroyl sarcosine; and 5% N-lauroyl sarcosine-0.1 M phosphate buffer [pH, 8.0]) in a 2-ml screw-cap tube containing 1 g of glass beads (0.1mm BioSpec Products, Inc., United States). This mixture was vortexed vigorously and subsequently incubated at 70°C for 1 h. After incubation by bead beating for 10 min at maximum speed, the extracted DNA was stored at -20 °C for further analysis.

PCR amplification

The V3-V4 region of the bacterial 16S ribosomal RNA gene from each sample was amplified using the universal bacterial primers F1 and R2 (5'-CCTACGGGNGGCWGCAG-3' and 5'-GACTACHVGGGTATCTAATCC-3'); these primers correspond to positions 341 to 805 in the Escherichia coli 16S rRNA gene. The PCR reactions were run in a T100™ Thermal Cycler PCR system (Bio-Rad Laboratories, Inc., United States) using the following protocol: 3 min of denaturation at 95 °C, followed by 21 0.5-min denaturation cycles at 94 °C, 0.5 min of annealing at 54 °C, and 0.5 min of elongation at 72 °C, with a final 5 min extension at 72 °C.

Sequencing

The amplicons from different samples were purified using Hieff NGS[®] DNA Selection Beads (Yeast-Biotech Co., Ltd., Shanghai, China). The products were indexed and mixed at equal ratios for sequencing by Shanghai Mobio Biomedical Technology Co., Ltd. using the Miseq platform (Illumina Inc., United States) according to the manufacturer's instructions.

Data availability

The raw sequencing data from the 16S rRNA gene V3-V4 regions and the accompanying information

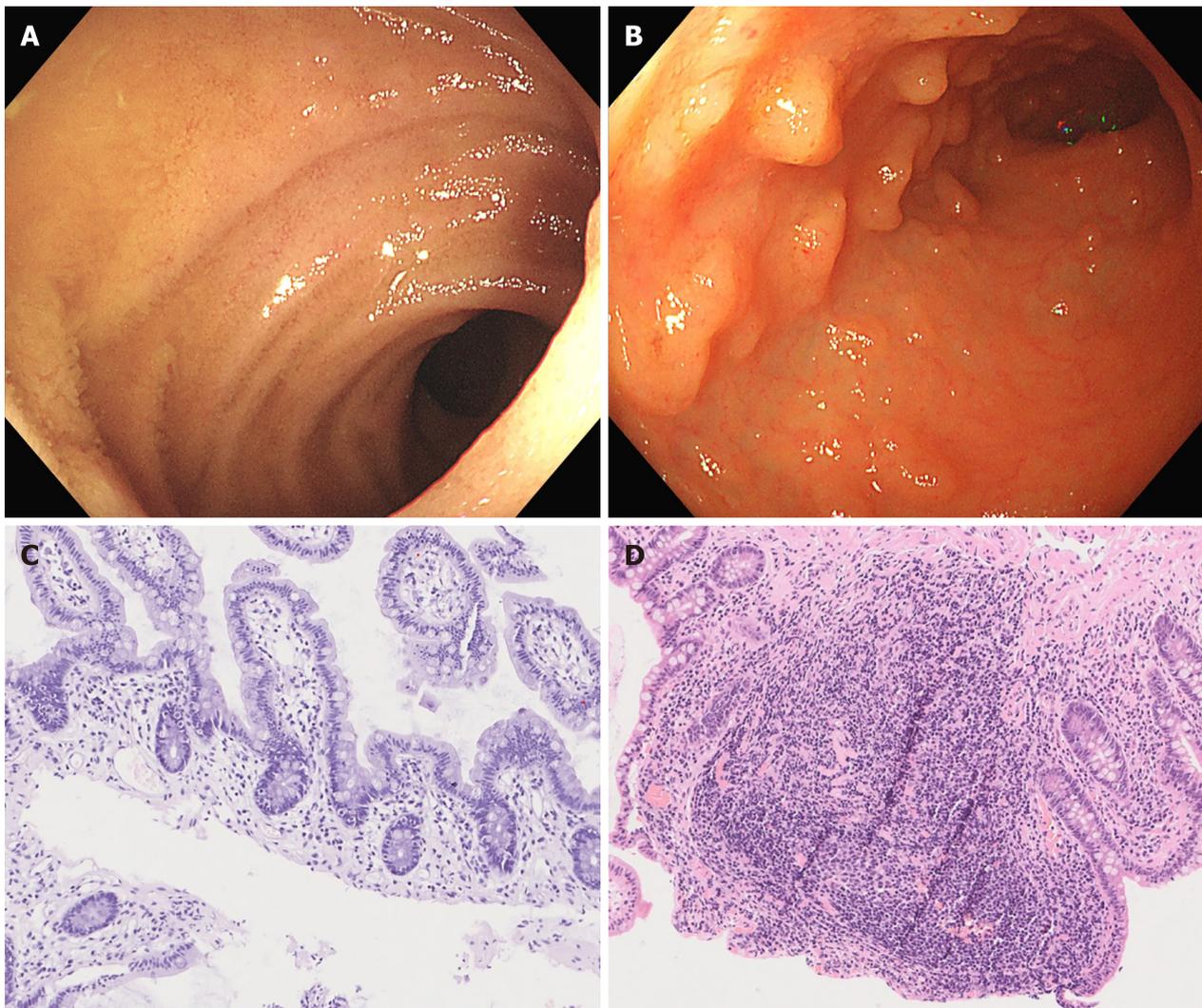


Figure 1 Endoscopic images and pathological characteristics of nodular lymphoid hyperplasia and normal mucosa in the terminal ileum. A: Endoscopic image of a normal terminal ileum from a healthy volunteer; B: Endoscopic image of nodular lymphoid hyperplasia (NLH) in terminal ileum of a patients; C: Pathological characteristics of normal terminal ileal mucosa ($\times 100$; scale bar, 200 μm); D: Pathological characteristics of terminal ileal NLH: hyperplastic lymphoid follicles germinal centers ($\times 100$; scale bar, 200 μm).

are available in the Sequence Read Archive database under accession number PRJNA759383.

Bioinformatics analysis

Clean data was extracted from the raw data using USEARCH version 11.0.667 (<http://www.drive5.com/usearch/>). Quality-filtered sequences were clustered into unique sequences and sorted in order of decreasing abundance to identify representative sequences using UPARSE according to the UPARSE Operational Taxonomic Units (OTUs) analysis pipeline, with singletons being omitted. OTUs were classified based on a 97% similarity after the chimeric sequences were removed using UPARSE version 7.1 (<http://drive5.com/uparse/>), after which they were annotated using the SILVA reference database (SSU138). The number of common OTUs in both groups was calculated and the results were shown using a Venn diagram.

Alpha diversity, which reflects the diversity of microbiome community, was obtained by analyzing the ACE estimator, Chao 1 estimator, Shannon-Wiener diversity index, and Simpson diversity index using Mothur version 1.42.1. The larger the Chao 1 or ACE index, the higher the gut flora abundance, whereas the higher the Shannon or Simpson index, the higher the community diversity.

To visualize the structural diversity of the gut microbiome in the discovery group, we used a principal coordinates analysis (PCoA) and nonmetric multidimensional scaling (NMDS) plots based on the Bray-Curtis distances. The corresponding statistical significance of the beta diversity was measured separately using an Adonis analysis.

To compare the microbial communities at each taxonomic level between the groups, significant between-group differences in the microbial composition were analyzed using a Wilcoxon rank-sum test. A linear discriminant analysis effect size (LEfSe) was used to show the maximum difference in the microbial structures between the groups (LEfSe version 1.1, <https://github.com/SegataLab/Lefse>) to

determine the specific bacterial taxa and predominant bacteria that are related to terminal ileal NLH. The results of the microbiome heatmap analysis, as provided by a random forests model, revealed a discriminatory intestinal microbiome between the two groups.

The Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) 2 version 2.4.1 (<https://github.com/picrust/picrust2/wiki>) was used to predict different metabolic pathways and orthologous groups between the groups according to the yoto Encyclopedia of Genes and Genomes (KEGG) database.

Statistical analysis

Non-parametric Mann-Whitney U tests were used to determine if there were significant differences between the groups. A Student's t-test was performed using SPSS for Windows, version 20.

RESULTS

OTU clustering and alpha diversity analysis of the mucosal intestinal microflora

In total, 1530914 usable sequences were obtained from 30 samples using Illumina high-throughput sequencing technology. From these, 1263179 high-quality sequences were selected, with an average of 42106 sequences per sample. Using 97% as the similarity cutoff, we generated 554 OTUs. The Venn diagram showed that 500 of the 554 OTUs were shared by both groups, whereas 33 OTUs were unique to the test group, and 21 were specific to the control group (Figure 2A).

The alpha diversity of the intestinal mucosal microflora was higher for the test group than it was for the control group. As estimated by the observed OTUs in each sample and the ACE and Chao indexes, which reflect the richness of the species diversity, the microbial diversity was significantly higher in the test group than it was in the control group ($P < 0.05$). The index values for the alpha diversity analysis are shown in Figures 2B-F.

The resulting rarefaction curves indicate that the microbial richness of the sampled guts was near saturation at the applied sequencing depth, which was sufficient to identify most of the bacterial community members in each individual. The Shannon-Wiener curve based on the OTUs was already flat, indicating that our sequencing depth was already adequate. The specaccum species accumulation curves revealed that the OTU richness approached saturation in all the samples (Supplementary Figure 1).

Analysis of the beta diversity based on OTU levels

To evaluate the similarities between all samples, the ecologic distances, which were calculated based on the Bray-Curtis distances, were visualized using a PCoA plot. A certain tendency of separation was found between both groups, indicating that the bacterial flora differences in the overall structure of gut microbiota existed between the groups (Figure 3A). Moreover, a non-metric multidimensional scaling analysis based on the Bray-Curtis distances showed a significant difference in gut microbiomes between both groups (Figure 3B).

Additionally, an Adonis analysis showed that there was a significant difference between the two groups ($P < 0.05$). Based on the unweighted and weighted UniFrac distances, a PCoA also showed that the microbial composition of the test group deviated from the control group (Adonis: $P = 0.0142$ and $P = 0.0467$, respectively).

Flora composition in the two sample groups

A total of 19 phyla were detected by classifying the species of all OTUs in the terminal ileal mucosa. At the phylum level, the gut microbiota of both groups was dominated by Bacteroidetes and Firmicutes, followed by (on average) Proteobacteria. The proportions of dominant flora in the test group were 35.19%, 39.29%, and 14.31% respectively, while those of the control group were 46.11%, 36.68%, and 8.34%, respectively. The average relative abundance of the microbiome at the phylum level is shown in Figure 4A.

At the genus level, the gut microbiota was dominated by *Bacteroides* in the control group, followed by *Faecalibacterium*, *Fusobacterium*, *Escherichia-Shigella*, and *Prevotella* with proportions of 36.85%, 8.47%, 6.93%, 4.96%, and 4.33%, respectively. Correspondingly, *Bacteroides* was the most dominant bacteria in the test group, followed by *Prevotella*, *Faecalibacterium*, *Fusobacterium*, and *Escherichia-Shigella*, with proportions of 19.63%, 10.31%, 8.39%, 8.33%, and 7.43%, respectively. The average relative abundance of the microbiome at the genus level is shown in Figure 4B.

Differences in microbiome compositions between the groups

There were significant differences in the microbial composition between the groups, as analyzed by the Wilcoxon rank-sum test. At the phylum level, Bacteroidetes were significantly lower in the test group than in the control group. In contrast, Patescibacteria and Campilobacterota were significantly higher in the test group than in the control group. At the genus level, the number of *Bacteroides* was significantly

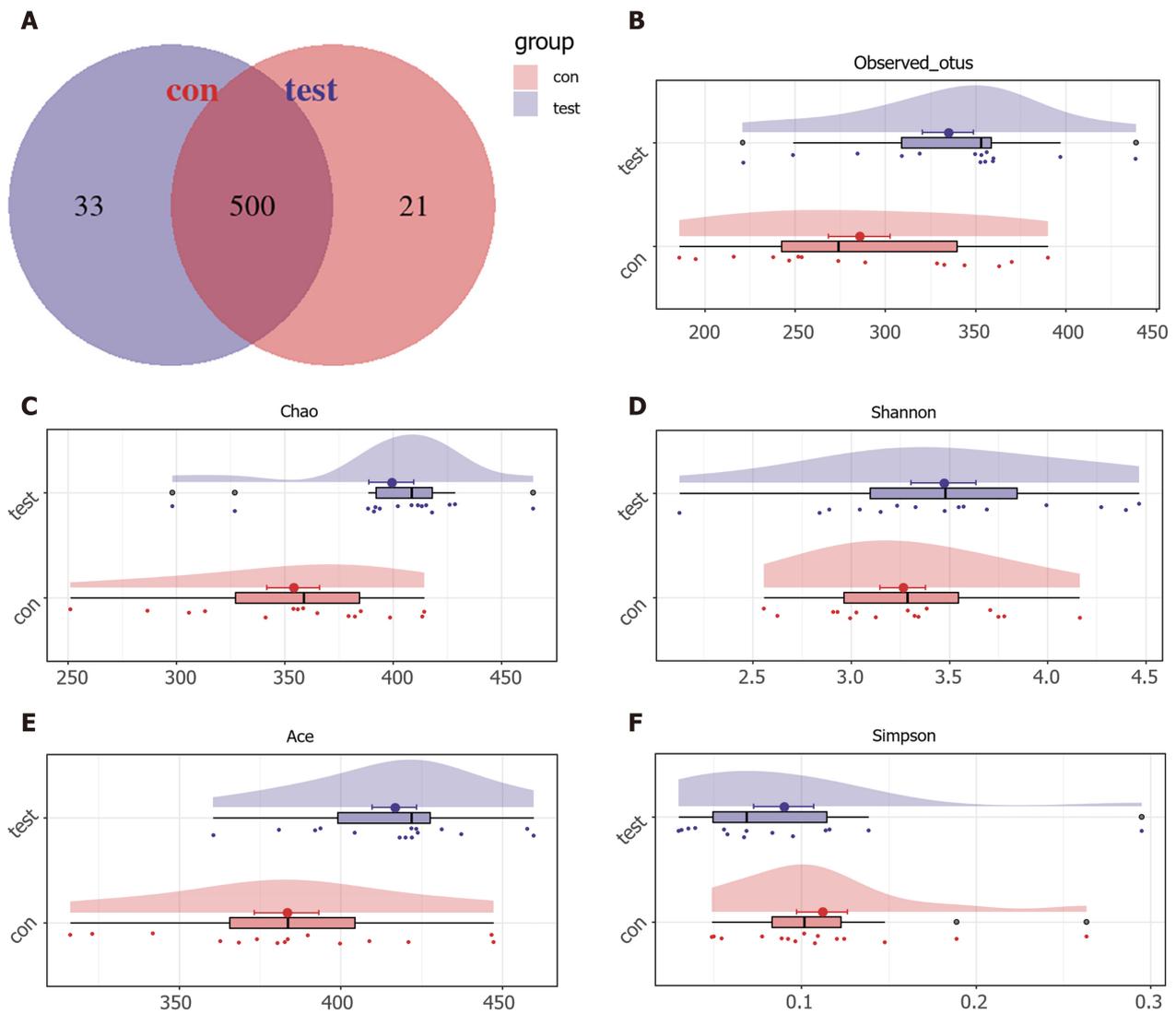


Figure 2 Operational Taxonomic Units clustering and alpha diversity analysis of mucosal intestinal microflora. A: Venn diagram demonstrates the shared and unique Operational Taxonomic Units (OTUs) in both groups; B: The OTUs in the single sample from each group; C: Chao index; D: Shannon-Wiener diversity index; E: ACE estimator; F: Simpson diversity index.

lower in the test group than in the control group. Conversely, the abundances of *Haemophilus*, *Streptococcus*, *Pseudomonas*, *Actinomyces*, TM7X, *Parvoimonas*, *Granulicatella*, *Helicobacter* and the [*Eubacterium*] *nodatum* group, among others, were significantly higher in the test group than in the control group (Figures 4C and D).

A LefSe was used to show the maximum difference in microbial structures between the groups to determine the specific bacterial taxa and predominant bacteria in the patients with terminal ileal NLH. This analysis showed that the abundances of various genera, including *Haemophilus*, *Streptococcus*, *Phocaea*, *Candidatus_saccharimonas*, *Pseudomonas*, *Vagococcus*, *Cutibacterium*, *Actinomyces*, the *Eubacterium nodatum* group, TM7X, *Delftia*, *Chryseobacterium*, *Peptostreptococcus*, *Helicobacter*, *Parvoimonas*, *Solobacterium*, and *Peptococcus*, among others, were significantly higher in the test group than in the control group. Conversely, the abundances of *Bacteroides*, *Bilophila*, and the [*Eubacterium hallii* group were significantly higher in the control group than in the test group (Figure 4E).

The results of the heatmap analysis of the microbiomes using a random forest model revealed a discriminatory intestinal microbiome between both groups. A total of 28 OTUs were found to be different between the sample groups. Among these OTUs, 24 were more abundant in the test group than in the control group; these OTUs belonged to the genera of *Rothia*, *Roseburia*, *Cutibacterium*, *Peptococcus*, *Parabacteroides*, *Lachnoanaerobaculum*, *Actinomyces*, *Streptococcus* and *Saccharimonadales*, *Solobacterium*, *Peptostreptococcus*, *Granulicatella*, *Parvoimonas*, *Lachnoclostridium*, *Pseudomonas*, *Fusobacterium*, *Haemophilus*, *Prevotella*, and *Clostridia* UCG-014. *Bacteroides*, *Bilophila*, and the [*Eubacterium*] *Siraenum* group were more abundant in the control group than in the test group (Figure 4F).

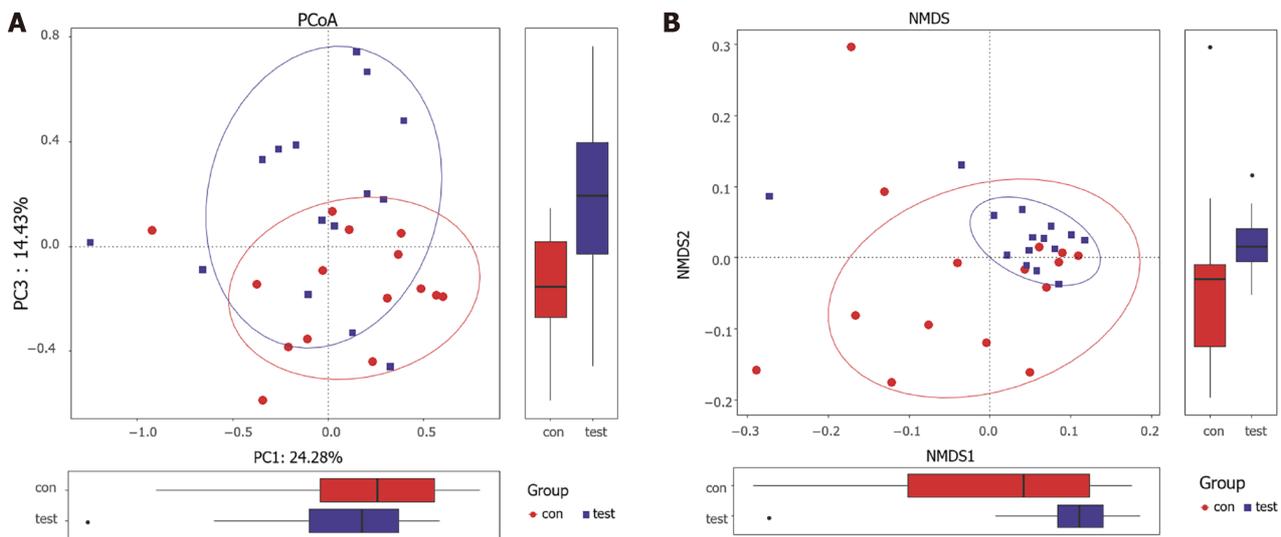


Figure 3 Analysis of beta diversity based on Operational Taxonomic Units levels. A: Principal coordinates analysis plots based on the Bray-Curtis distances shows the differences in the bacterial flora between the terminal ileal nodular lymphoid hyperplasia and control groups; B: Nonmetric multidimensional scaling analysis based on the Bray-Curtis distances shows the differences between both groups. Each symbol represents one sample.

Functional alterations of gut microbiomes in both groups

PICRUSt2 version 2.4.1 was used to predict metabolic pathways and orthologous groups according to the KEGG database, and a LefSe was subsequently used to sort the different metabolic pathways and orthologous groups between the two groups. The results demonstrated that Photosynthesis, D Alanine metabolism, C5 Branched dibasic acid metabolism, Peptidoglycan biosynthesis, Aminoacyl tRNA biosynthesis, Bacterial chemotaxis, ABC transporters, D glutamine and D glutamate metabolism, synthesis and degradation of ketone bodies, sulfur relay system, ribosome, mismatch repair, homologous recombination, Glycerophospholipid metabolism, base excision repair, DNA replication, butanoate metabolism, bacterial secretion system, terpenoid backbone biosynthesis, and styrene degradation were significantly higher in test group compared to the control group. However, glycosaminoglycan degradation, secondary bile acid biosynthesis, sphingolipid metabolism, biotin metabolism, pentose and glucuronate interconversions, galactose metabolism, streptomycin biosynthesis, cyanoamino acid metabolism, and alanine aspartate and glutamate metabolism pathways were all significantly higher in the control group than in the test group. Altered metabolic pathways, orthologous groups, and modules in both groups are presented in [Figure 5](#).

DISCUSSION

Terminal ileal NLH is commonly detected through colonoscopy. The pathogenesis of terminal ileal NLH remains unclear, it is generally regarded that infection-induced immune responses play a key role. Alterations of the gut microbiota are closely related to immune-related diseases. However, whether the gut flora plays a role in terminal ileal NLH is unclear. Currently, there are no studies that have reported on the relationship between the intestinal flora and terminal ileal NLH. In this study, alpha diversity was higher in the test group than in the control group. *Helicobacter*, *Fusobacterium nucleatum*, *Actinomyces*, *TM7X*, and *Peptostreptococcus* were significantly more abundant in the test group than in the control group. Additionally, the Peptidoglycan and Aminoacyl tRNA biosynthesis pathways were significantly more abundant in the test group than in the control group.

In this study, we found that the bacterial diversity was significantly higher in the terminal ileal NLH group than in the control group, suggesting the presence of a small intestinal bacterial overgrowth (SIBO). SIBO is defined as bacterial overgrowth in the small intestine caused by an abnormally high number of bacteria and/or changes in the kinds of bacteria; it is accompanied by an overgrowth of bacteria in the small bowel in excess of 10^5 colony forming units per milliliter in upper gut aspirate culture[14]. This is due to the bacteria migrating into the small intestine from distal intestinal tract, resulting in intestinal mucosal inflammation and permeability and villi damage, which mainly manifests as nutrient malabsorption, abdominal pain and distension, diarrhea, and intestinal motility abnormality[15]. SIBO is closely associated with many diseases, including colorectal cancer, irritable bowel syndrome, inflammatory bowel disease, and non-alcoholic fatty liver disease[16-19]. In this study, we found an increased alpha diversity of intestinal flora in the test group than in the control group. This observation may be related to the local inflammatory response caused by the overgrowth of intestinal

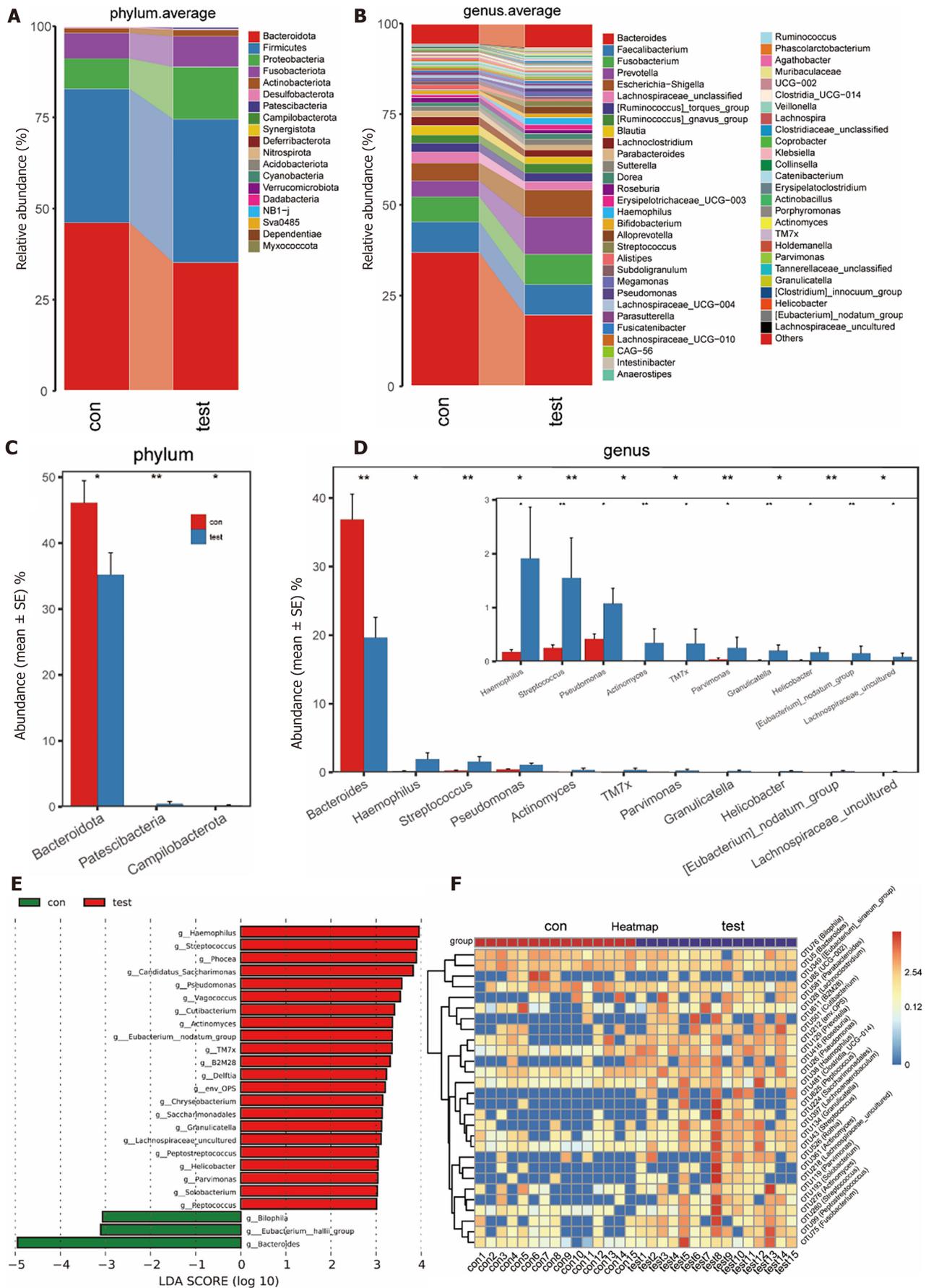


Figure 4 Flora composition and comparison of microbiome composition in both groups. A: Flora composition at the phylum level; B: Flora composition at the genus level; C: The abundance of Bacteroidetes was significantly lower at the phylum level in the test group, as assessed by a Wilcoxon rank-sum test; D: Differences in the flora at the genus level between the groups, as assessed by a Wilcoxon rank-sum test; E: Flora differences at the genus level, as assessed

by Linear discriminant analysis effect size; F: A heatmap analysis of the microbiomes using a random forest model.

bacteria, which results in NLH.

Bacteroidetes and Firmicutes make up most of the human intestinal flora, with a higher abundance of Bacteroidetes. In this study, Bacteroidetes and Firmicutes were the dominant bacteria in both groups, followed by Proteobacteria. Similarly, Bacteroides was the most dominant bacteria in both groups at the genus level. However, Bacteroidetes and Bacteroides were significantly less abundant in the test group than in the control groups, suggesting that Bacteroides may play a protective role in the development of terminal ileal inflammation and NLH.

In our research, *H.pylori* was higher in abundance in the test group. *H.pylori*, which is a proteobacteria, is considered to be a carcinogenic factor of gastric cancer. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is related to *H.pylori*[20,21], as most patients with MALT can achieve long-term clinical remission after *H.pylori* eradication[22,23]. *H.pylori* is thought to be an antigenic stimulant that can activate the NF- κ B pathway[24] and induce pro-inflammatory cytokines expression [25,26]. Persistent inflammation promotes the formation of mucosal lymphoid follicles, typically consisting of B lymphocytes, which might contribute to the genesis of gastric MALT lymphoma once the inflammatory courses are uncontrolled[27]. Khuroo *et al* studied a large cohort of patients ($n = 40$) with NLH that was etiologically related to *H.pylori* infection. Compared with patients with consistent *H.pylori* infection, patients with eradicated *H.pylori* showed a significant clinical response and lesion regression/resolution [28]. However, the location was limited to the postbulbar duodenum (second and third parts) and duodenojejunal junction in these cases. In our study, the *H.pylori* abundance increased in test group. Moreover, it has been reported that NLH may be associated with an increased risk of parenteral lymphoma. However, currently, there are no relevant reports on the correlation and causal relationship between terminal ileal NLH and *H.pylori*, which is worthy of studying. When treating patients with *H.pylori*, we suggest that endoscopists should routinely observe the terminal ileum.

In this study, the abundance of Actinomycetes and TM7x increased in the test group. Actinomycetes mostly reside in the oral cavity, upper respiratory tract, digestive tract, and urogenital tract in humans and animals, as part of the normal flora. Actinomycetes are recognized to be a cause of chronic appendicitis. Actinomycetes are also associated with Crohn-like appendicitis with significant fibrosis, transmural inflammation, lymphoid hyperplasia, and granuloma[29]. TM7x is a saccharifying bacteria, which is a parasitic bacterium that interacts with core members of Actinomycetes. A previous study suggested that ultra-small bacteria may have the ability to regulate the immune response of normal hosts, and there was a signal overlap between TM7x and basibiont Actinomycetes odontolyticus species (XH001) by metabolic pathway prediction[30]. Moreover, through *in vitro* experiments, the authors demonstrated that TM7x inhibited TNF- α expression in XH001-induced macrophages[31]. Consequently, the interaction between Actinomycetes and TM7x may promote terminal ileal NLH.

In this study, we found that the abundance of *Fusobacterium nucleatum* increased in the test group, and this increase is possibly related to terminal ileal NLH. *Fusobacterium nucleatum* has been reported to be enriched in colorectal cancer tissues and played a crucial role in the occurrence and development of colorectal cancer[32]. It can adhere to and invade intestinal epithelial cells and activate the β -catenin pathway by releasing FadA adhesin and binding with cadherin E-cadherin, thus promoting inflammation and tumor response[33]. Recently, it has been reported that *Fusobacterium nucleatum* macromolecules (> 50 KDA) have a proinflammatory effect on human intestinal epithelium, and the outer membrane vesicles can promote the secretion of proinflammatory cytokines, including IL-8 and TNF α by epithelial cells[34]. Further animal experiments also verified the proinflammatory effect of *Fusobacterium nucleatum* on intestinal epithelium. Thus, *Fusobacterium nucleatum* may be associated with the development of terminal NLH.

In our study, the abundance of *Peptostreptococcus* increased in the test group. Anaerobic peptostreptococcus and *Peptostreptococcus magnus* are most commonly in the genus of *Peptostreptococcus*, among which Anaerobic peptostreptococcus is the most common pathogen. Anaerobic peptostreptococcus is a gram-positive anaerobic bacteria commonly residing in the oral cavity and digestive tract. The abundance of Anaerobic peptostreptococcus in the stool samples of patients with colorectal cancer was reported to be higher than healthy volunteers. *In vitro* studies have shown that Anaerobic digestion streptococcus interacts with TLR2 and TLR4 in colon cells and increases the level of active oxides, thereby promoting cholesterol synthesis and cell proliferation[35]. The PCWBR2 integrin $\alpha 2/\beta 1$ -PI3K-Akt-NF- κ B signal axis has been reported to be involved in the development of colorectal cancer[36]. *Peptostreptococcus* may be related to terminal ileal inflammation and NLH, although further confirmation of this is needed in the future.

Metabolic pathways, such as the Peptidoglycan biosynthesis and Aminoacyl tRNA biosynthesis, increased in the test group in the current study. Peptidoglycan, a bacterial cell wall component, is a conserved pathogen-associated molecule that is involved in the innate immune system because it recognizes pattern recognition receptors that are secreted and expressed in or on the cell surface[37]. Transfer RNAs (tRNAs) mainly participates in protein translation by transporting amino acids to the ribosome. Nevertheless, accumulating evidence has shown that tRNAs are closely associated with

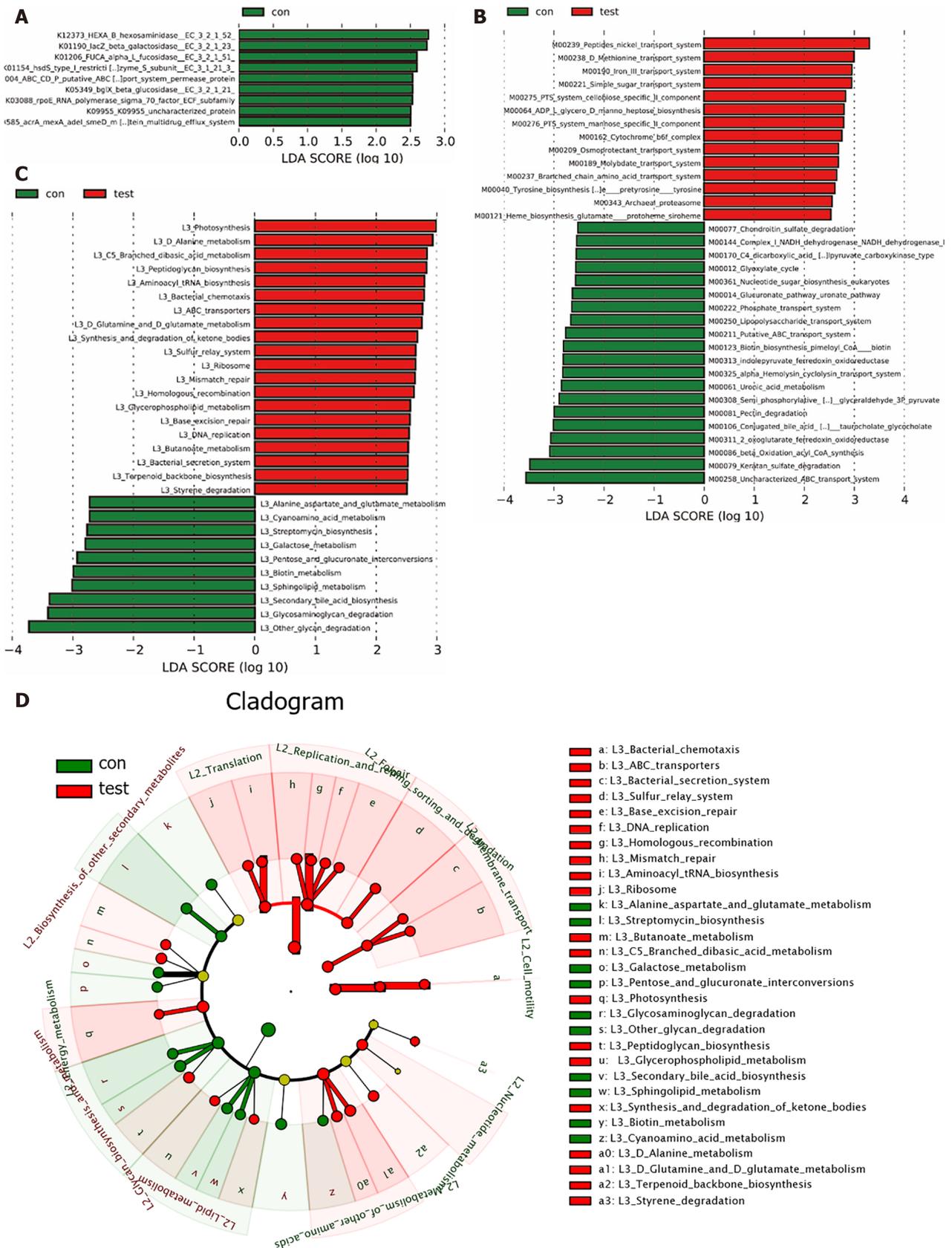


Figure 5 Predictions of the functional alteration to the gut microbiomes in patients with nodular lymphoid hyperplasia in the terminal ileum. A: Decreased the yoto Encyclopedia of Genes and Genomes orthologous groups in patients with terminal ileal nodular lymphoid hyperplasia (NLH) as shown by the histogram of the linear discriminant analysis (LDA) scores; B: Altered modules in patients with terminal ileal NLH (red, terminal ileal NLH tissue; green, control); C: Altered metabolic pathways in patients with terminal ileal NLH as shown by the histogram of the LDA scores (red, terminal ileal NLH tissue; green, control); D: Altered metabolic pathways in patients with terminal ileal NLH (red, terminal ileal NLH tissue; yellow, insignificant; green, control) as shown by a cladogram.

various physiological and pathological processes such as immune regulation. Aminoacyl-tRNA synthetases (ARSs) are essential components of translation in all living species, and it has taken scientists decades to confirm that eukaryotic ARSs act as global cell signaling mediators to regulate cell homeostasis beyond their intrinsic function as protein synthesis enzymes. Recent discoveries have revealed that ubiquitously expressed standby cytoplasmic ARSs sense and respond to danger signals and regulate immunity against infections, indicating their potential as therapeutic targets for infectious diseases[38,39]. Perhaps Peptidoglycan biosynthesis and Aminoacyl-tRNA biosynthesis might act as the targeted intervention sites.

The etiology of terminal ileal NLH has not been fully elucidated yet. In this study, we firstly analyzed the diversity and composition of intestinal flora in the mucosal tissues of the patients with terminal ileal NLH and predicted the metabolic pathways using 16S-rRNA technology. We subsequently found that terminal ileal NLH was related to the disturbance of the intestinal flora and certain microflora might act on the small intestinal mucosa thereby causing terminal ileal NLH. Moreover, the metabolic pathways that were predicted using PICRUSTs are possibly involved in terminal ileal NLH, which provides novel ideas for further exploration of potential molecular mechanisms. Diarrhea was frequently commonly found in patients with terminal ileal NLH, and some patients may get a satisfactory effect through probiotic supplementation. Therefore, exploring intestinal flora changes, seeking related bacteria genera in patients with terminal ileal NLH, and supplementing targeted protective bacteria or clearing targeted bacteria may reduce the risk of lymphoma and improve patient symptoms.

This study has some limitations. First, the sample size was relatively small. Although our preliminary results reveal that there was a significant difference between the two groups, studies with larger sample sizes covering different regions and populations are necessary to confirm the findings. Second, the male-female ratio in the NLH group was not balanced in this study due to the nature of terminal ileal NLH, which is thought to be significantly more common in men than women. Although the incidence of terminal ileal NLH in both men and women has not been investigated through a large-scale study, Lin *et al* observed that males outnumbered females by approximately four to one in a small-scale study[3]; their results support, to a certain degree, the suggestion that there is a higher frequency of terminal ileal NLH in males than females. We also performed a correlation analysis to compare the intestinal flora with gender using the Multivariable Association with Linear Models2, and we found that there was no correlation between the intestinal floras and gender at the phylum, genus, or OTU levels. To obtain more rigorous results, we will perform a large-scale study and ensure that there is an equal gender ratio among groups. Third, this study was only a preliminary correlation analysis between the intestinal flora and terminal ileal NLH, and no further research on the related mechanisms was performed. Further studies using animal testing *in vivo* and *in vitro* cellular experiments can be developed once our findings are verified in larger populations.

CONCLUSION

Intestinal flora disturbances are related to terminal ileal NLH, and our results show that certain microflora may act on the small intestinal mucosa and cause terminal ileal NLH. Maintaining the intestinal flora balance and supplementing targeted protective bacteria could improve terminal ileal NLH symptoms and potentially reduce the risk of lymphoma transformation.

ARTICLE HIGHLIGHTS

Research background

Nodular lymphoid hyperplasia (NLH) in the small intestine is a rare benign lesion characterized by multiple small nodules on the intestinal surface. NLH is linked to the immune system, and it may result from accumulation of plasma-cell precursors due to a maturational defect during the development of B lymphocytes. The intestinal microbiome plays an essential role in the immune system. However, whether the gut flora plays a role in NLH is unclear.

Research motivation

To explore the correlation between intestinal flora and terminal ileal NLH and predict the metabolic pathways that are involved in terminal ileal NLH.

Research objectives

To investigate the characteristics of the mucosal microbiota in patients with terminal ileal NLH for seeking related bacteria genera and bringing a new idea for related mechanisms.

Research methods

A total of 30 patients who underwent a colonoscopy were recruited for this study. A total of 15 Patients with terminal ileal NLH were assigned to the test group, while 15 healthy volunteers were assigned to the control group after undergoing a routine physical examination. We collected mucosal biopsy samples that were obtained *via* colonoscopy from both groups. We subsequently performed 16S-rRNA gene amplicon sequencing of these samples, and the results were evaluated using alpha diversity, beta diversity and microbial composition analyses. The Phylogenetic Investigation of Communities by Reconstruction of Unobserved States was used to predict the metabolic pathways and orthologous groups according to the Kyoto Encyclopedia of Genes and Genomes database.

Research results

The terminal ileal NLH group showed an increased alpha diversity. The overall intestinal microbiota in the NLH group was significantly different from that of the control group. The relative abundance of phylum Bacteroidetes was significantly lower in the NLH group, while that of Patescibacteria and Campilobacterota was significantly higher. The abundance of the genus *Bacteroides* was significantly lower in the test group. Conversely, the relative abundances of *Haemophilus*, *Streptococcus*, *Pseudomonas*, *Actinomyces*, *TM7X*, *Fusobacterium nucleatum*, *Parvimonas*, *Granulicatella*, *Helicobacter*, and the [*Eubacterium*] *nodatum* group were significantly higher in the test group. Metabolic pathways such as Peptidoglycan biosynthesis and Aminoacyl tRNA biosynthesis were both increased in the test group.

Research conclusions

Maintaining the microbial balance and supplementing targeted protective bacteria could improve symptoms and potentially reduce the risk of lymphoma transformation in patients with terminal ileal NLH.

Research perspectives

Further research on the related mechanisms was needed to be performed in future. Further studies using animal testing *in vivo* and *in vitro* cellular experiments can be developed once our findings are verified in larger populations.

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FOOTNOTES

Author contributions: Jiang QL and Lu Y equally contributed on this manuscript, designed and conceived the experiments; Lu Y and Li WH collected patient samples and data; Jiang QL, Zhang MJ, Cui ZY and Pei ZM performed the 16S rRNA sequencing data analysis; Jiang QL and Lu YY acquired and analyzed data, wrote the manuscript; Lu YY and Wang JJ provided guidance for sample processing methodology; Lu LG reviewed the manuscript; all authors approved the final version of the article.

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