

World Journal of *Clinical Cases*

World J Clin Cases 2019 September 26; 7(18): 2658-2915



**OPINION REVIEW**

- 2658** Effective use of the Japan Narrow Band Imaging Expert Team classification based on diagnostic performance and confidence level
Hirata D, Kashida H, Iwatate M, Tochio T, Teramoto A, Sano Y, Kudo M

MINIREVIEWS

- 2666** Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet in children
Fodor I, Man SC, Dumitrascu DL
- 2675** High-resolution colonic manometry and its clinical application in patients with colonic dysmotility: A review
Li YW, Yu YJ, Fei F, Zheng MY, Zhang SW

ORIGINAL ARTICLE**Retrospective Study**

- 2687** Predictors of rebleeding and in-hospital mortality in patients with nonvariceal upper digestive bleeding
Lazăr DC, Ursoniu S, Goldiș A
- 2704** Analgesic effect of parecoxib combined with ropivacaine in patients undergoing laparoscopic hepatectomy
Huang SS, Lv WW, Liu YF, Yang SZ
- 2712** Prognostic significance of 14v-lymph node dissection to D2 dissection for lower-third gastric cancer
Zheng C, Gao ZM, Sun AQ, Huang HB, Wang ZN, Li K, Gao S

Observational Study

- 2722** Wall shear stress can improve prediction accuracy for transient ischemic attack
Liu QY, Duan Q, Fu XH, Jiang M, Xia HW, Wan YL

Prospective Study

- 2734** Characterization of microbiota in systemic-onset juvenile idiopathic arthritis with different disease severities
Dong YQ, Wang W, Li J, Ma MS, Zhong LQ, Wei QJ, Song HM

SYSTEMATIC REVIEWS

- 2746** Sinusoidal obstruction syndrome: A systematic review of etiologies, clinical symptoms, and magnetic resonance imaging features
Zhang Y, Jiang HY, Wei Y, Song B

META-ANALYSIS

- 2760 Respiratory training interventions improve health status of heart failure patients: A systematic review and network meta-analysis of randomized controlled trials
Wang MH, Yeh ML

CASE REPORT

- 2776 *Mycobacterium chimaera* infections following cardiac surgery in Treviso Hospital, Italy, from 2016 to 2019: Cases report
Inojosa WO, Giobbia M, Muffato G, Minniti G, Baldasso F, Carniato A, Farina F, Forner G, Rossi MC, Formentini S, Rigoli R, Scotton PG
- 2787 Giant squamous cell carcinoma of the gallbladder: A case report
Junior MAR, Favaro MDL, Santin S, Silva CM, Iamarino APM
- 2794 Liver re-transplantation for donor-derived neuroendocrine tumor: A case report
Mrzljak A, Kocman B, Skrtic A, Furac I, Popic J, Franusic L, Zunec R, Mayer D, Mikulic D
- 2802 Calcifying fibrous tumor originating from the gastrohepatic ligament that mimicked a gastric submucosal tumor: A case report
Kwan BS, Cho DH
- 2808 Pancreatitis, panniculitis, and polyarthritides syndrome caused by pancreatic pseudocyst: A case report
Jo S, Song S
- 2815 Glomus tumor of uncertain malignant potential of the brachial plexus: A case report
Thanindrarn P, Chobpenthai T, Phorkhar T, Nelson SD
- 2823 Conservative pulp treatment for Oehlers type III dens invaginatus: A case report
Lee HN, Chen YK, Chen CH, Huang CY, Su YH, Huang YW, Chuang FH
- 2831 Propofol pump controls nonconvulsive status epilepticus in a hepatic encephalopathy patient: A case report
Hor S, Chen CY, Tsai ST
- 2838 Teriparatide as nonoperative treatment for femoral shaft atrophic nonunion: A case report
Tsai MH, Hu CC
- 2843 Successful repair of acute type A aortic dissection during pregnancy at 16th gestational week with maternal and fetal survival: A case report and review of the literature
Chen SW, Zhong YL, Ge YP, Qiao ZY, Li CN, Zhu JM, Sun LZ
- 2851 Inferior pancreaticoduodenal artery pseudoaneurysm in a patient with calculous cholecystitis: A case report
Xu QD, Gu SG, Liang JH, Zheng SD, Lin ZH, Zhang PD, Yan J

- 2857** ALK-positive anaplastic large cell lymphoma of the thoracic spine occurring in pregnancy: A case report
Yang S, Jiang WM, Yang HL
- 2864** Endoscopic mucosal resection of a bile duct polyp: A case report
Yang S, Yang L, Wang XY, Yang YM
- 2871** Multiple gastric adenocarcinoma of fundic gland type: A case report
Chen O, Shao ZY, Qiu X, Zhang GP
- 2879** Repair of the portal vein using a hepatic ligamentum teres patch for laparoscopic pancreatoduodenectomy: A case report
Wei Q, Chen QP, Guan QH, Zhu WT
- 2888** Drug coated balloon angioplasty for renal artery stenosis due to Takayasu arteritis: Report of five cases
Bi YH, Ren JZ, Yi MF, Li JD, Han XW
- 2894** Entrapment of the temporal horn secondary to postoperative gamma-knife radiosurgery in intraventricular meningioma: A case report
Liu J, Long SR, Li GY
- 2899** Pleomorphic lipoma in the anterior mediastinum: A case report
Mao YQ, Liu XY, Han Y
- 2905** Guillain-Barré syndrome in a patient with multiple myeloma after bortezomib therapy: A case report
Xu YL, Zhao WH, Tang ZY, Li ZQ, Long Y, Cheng P, Luo J
- 2910** Bowen's disease on the palm: A case report
Yu SR, Zhang JZ, Pu XM, Kang XJ

ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes case reports, case series, and articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics including diagnostic, therapeutic, and preventive modalities.

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Prospective Study

Characterization of microbiota in systemic-onset juvenile idiopathic arthritis with different disease severities

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statement: This study was reviewed and approved by the Ethics Committee of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Informed consent statement:

Written informed consent was obtained from one of the parents of each participant on the day of sample collection.

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Abstract

BACKGROUND

Systemic-onset juvenile idiopathic arthritis (SoJIA) is one of most serious subtypes of juvenile idiopathic arthritis. Although the pathogenesis of SoJIA remains unclear, several studies have suggested a correlation between gut dysbiosis and JIA. Further understanding of the intestinal microbiome may help to establish alternative ways to treat, or even prevent, the disease.

AIM

To explore alterations in fecal microbiota profiles in SoJIA patients and to evaluate the correlations between microbiota and clinical parameters.

METHODS

We conducted an observational single-center study at the Pediatric Department of Peking Union Medical College Hospital. Children who were diagnosed with SoJIA at our institution and followed for a minimum period of six months after diagnosis were recruited for the study. Healthy children were recruited as a control group (HS group) during the same period. Clinical data and stool samples were collected from SoJIA patients when they visited the hospital.

RESULTS

The SoJIA group included 17 active and 15 inactive consecutively recruited children; the control group consisted of 32 children. Firmicutes and Bacteroidetes were the two most abundant phyla among the total sample of SoJIA children and controls. There was a significant difference among the three groups in observed species, which was the highest in the Active-SoJIA group, followed by the Inactive-SoJIA group and then HS group (Active-SoJIA *vs* HS: $P = 0.000$; and Inactive-SoJIA *vs* HS: $P = 0.005$). We observed a lower Firmicutes/Bacteroidetes ratio in SoJIA patients (3.28 ± 4.47 in Active-SoJIA, 5.36 ± 8.39 in Inactive-SoJIA,

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and 5.67 ± 3.92 in HS). We also observed decreased abundances of Ruminococcaceae (14.9% in Active-SoJIA, 17.3% in Inactive-SoJIA, and 22.8% in HS; Active-SoJIA vs HS: $P = 0.005$) and Faecalibacterium (5.1% in Active-SoJIA, 9.9% in Inactive-SoJIA, and 13.0% in HS; Active-SoJIA vs HS: $P = 0.000$) in SoJIA compared with HS. By contrast, the abundance of Bacteroidaceae was the highest in the Active-SoJIA group, followed by the Inactive-SoJIA and HS groups (16.5% in Active-SoJIA, 12.8% in Inactive-SoJIA, and 9.7% in HS; Active-SoJIA vs HS: $P = 0.03$). The Spearman correlation analysis revealed a negative correlation between Proteobacteria or Enterobacteriaceae and juvenile arthritis disease activity score on 27 joints (JADAS-27).

CONCLUSION

The composition of the intestinal microbiota is different in SoJIA patients compared with healthy children. The dysbiosis presents partial restoration in inactive status patients.

Key words: Microbiota; Systemic-onset juvenile idiopathic arthritis; Disease activity; Dysbiosis

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Core tip: In recent decades, the potential role of gut microbiome in modulating host homeostasis has gained considerable attention. This is the first report of microbiota composition in systemic-onset juvenile idiopathic arthritis (SoJIA) children. Our results demonstrate that the composition of the intestinal microbiota is different in SoJIA patients compared with healthy children. The perturbed microbiota present partial restoration in inactive status patients. Characterizing intestinal microbiomes may help to understand the pathogenesis of SoJIA. Modifications of the microbiota may be a new way of preventing and managing SoJIA.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory joint disease in children^[1]. According to the International League of Associations for Rheumatology (ILAR) classification criteria, there are seven different JIA categories: Systemic-onset juvenile idiopathic arthritis (SoJIA), oligoarticular arthritis (affecting less than four joints at onset), polyarticular arthritis (affecting more than four joints at onset), rheumatoid factor negative and positive arthritis, enthesitis-related arthritis (ERA), psoriatic arthritis, and undifferentiated arthritis. SoJIA is the most severe subtype among the seven subtypes of JIA, distinguished from other subtypes by its predominant systemic inflammation and extraarticular features, including spiking fevers, macular rash, lymphadenopathy, hepatosplenomegaly, and serositis^[3]. Although the pathogenesis of SoJIA remains unclear, it is widely believed that complex interactions between host genetics, immunological dysregulation, and environmental influences (lifestyle, diet, antibiotics, and infections) are involved^[4].

In recent decades, the potential role of the gut microbiome in modulating host homeostasis has gained considerable attention^[5]. There is an increasing number of studies revealing the presence of gut dysbiosis in various diseases, such as inflammatory bowel disease, arthritis, multiple sclerosis, systemic lupus erythematosus, and type 2 diabetes^[6-10]. Understanding of the intestinal microbiome may help to establish alternative ways to treat, or even prevent, these diseases. However, data regarding the role of the intestinal microbiota in JIA patients are not conclusive and changes in gut microbes over the JIA disease course remain uncertain. To date, there are no studies on gut microbiota in SoJIA children. Therefore, we used fecal samples to characterize the intestinal microbiomes of SoJIA patients and healthy

children. In order to understand the changes in the gut microbiome in different disease states, we also compared the microbiota composition in active-SoJIA patients versus inactive-SoJIA patients. Correlations between the gut microbiota composition and clinical parameters of disease activity were also evaluated.

MATERIALS AND METHODS

Ethical considerations

The protocol for this study was approved by the local ethics committee of the Peking Union Medical College Hospital (Protocol number: JS-1659). Written informed consent was obtained from one of the parents of each participant on the day of sample collection. All procedures were performed in accordance with the Declaration of Helsinki.

Sampling of subjects

Children who were diagnosed with SoJIA according to the ILAR classification criteria and followed for a minimum period of six months were recruited from the Peking Union Medical College Hospital^[2]. During the same period, healthy children were recruited as a control group. Inactive disease (ID) status was defined according to the Wallace criteria: No active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; no abnormal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); best possible physician's global assessment (PGA) disease activity score^[11]. Patients suffering from cancer, heart failure, renal failure, chronic infectious disease, macrophage activation syndrome (MAS), and overlapping other rheumatic immune diseases were all excluded. Individuals were also excluded if they had received antibiotics or had a symptomatic gastrointestinal infection within one month prior to participating in this study.

Initially, from June 1, 2017 to December 31, 2018, a total of 33 patients with SoJIA agreed to participate in this study; however, one patient was excluded from the study because of comorbid systemic lupus erythematosus (SLE) during follow-up. Therefore, a total of 32 patients with SoJIA were investigated. The control group comprised 32 children aged from 5 to 16 years. Patients were divided into two groups according to activity status at the time of sample collection: 17 were classified as active SoJIA and 15 were inactive. Clinical data and stool samples were collected from the SoJIA patients when they visited the hospital. Each stool specimen was collected in a sterile vial; it was then transported immediately to the laboratory and frozen at -80 °C until analysis. Collected clinical data included age of onset, disease duration, active joint count (AJC), ESR, CRP, PGA, parent/patient visual analogue scale (VAS) of well-being, and juvenile arthritis disease activity score on 27 joints (JADAS-27)^[12].

DNA extraction and PCR amplification

Bacterial DNA was extracted at Beijing Novogene Bioinformatics Technology Co. Ltd using the SDS method. DNA concentration and purity were monitored on 1% agarose gels. Based on the initial concentration, DNA was diluted to 1 ng/μL using sterile water. The specific primers 515F (5'-GTGCCAGCMGCCGCGGTAA-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3') were used to amplify the V4 region of 16S rRNA genes. All PCR reactions were carried out in 30 μL reactions with 15 μL of Phusion® High-Fidelity PCR Master Mix (New England Biolabs, Ipswich, MA, United States), 0.2 μmol/L of forward and reverse primers, and about 10 ng of template DNA. Thermal cycling consisted of initial denaturation at 98 °C for 1 min, followed by 30 cycles of denaturation at 98 °C for 10 s, annealing at 50 °C for 30 s, and elongation at 72 °C for 30 s, with a final cycle of 72 °C for 5 min. The same volume of 1 × loading buffer (containing SYB green) was mixed with PCR products and electrophoresis was performed on 2% agarose gels for detection. Samples with a bright main band between 400-450 bp were chosen for further experiments. PCR products were mixed in equidensity ratios. Then, mixture PCR products were purified using a GeneJET Gel Extraction Kit (Thermo Scientific).

High-throughput sequencing analysis

Sequencing libraries were generated using a TruSeq® DNA PCR-Free Sample Preparation Kit, following the manufacturer's recommendations, and index codes were added. Library quality was assessed on a Qubit® 2.0 Fluorometer (Thermo Scientific) and Agilent Bioanalyzer 2100 system. Finally, the library was sequenced on an Illumina HiSeq 2500 and 250 bp paired-end reads were generated. Paired-end reads from the original DNA fragments were merged using FLASH and were then assigned to each sample according to the unique barcodes. Sequences were analyzed

using the QIIME software package (Quantitative Insights Into Microbial Ecology), and in-house Perl scripts were used to analyze alpha- (within samples) and beta- (among samples) diversity^[14]. Sequences with a $\geq 97\%$ similarity were assigned to the same operational taxonomic units (OTUs). For each representative sequence, the SILVA132 database was used to annotate taxonomic information.

Bioinformatics analysis

Alpha diversity analysis, including observed species, Chao1 index, Shannon index, Simpson index, and beta diversity, including both unweighted and weighted UniFrac distances, were performed with QIIME (version 1.9.1). Principal Coordinate Analysis (PCoA) was performed and displayed with the WGCNA package, stats package, and ggplot2 package in R software (version 2.15.3). The significance of between-group differences in UniFrac distances was assessed with PERMANOVA using the *adonis* function of the R package *vegan*. Correlations between gut microbiota composition and clinical parameters of disease activity were also evaluated.

Statistical analysis

Quantitative data are presented as the mean (SD) or median (IQR) in the case of skewed data. Qualitative data are presented as frequencies and proportions. When comparing continuous data between two groups, the Welch's test or Mann-Whitney *U* test was applied to calculate intergroup differences. Pearson chi-square test was employed for categorical variables. ANOVA was used for comparisons of parametric data among three groups. Differences in abundance of bacterial communities between Active-SoJIA, Inactive-SoJIA, and healthy subjects (HS) were tested by the Kruskal-Wallis test, and *P*-values with Bonferroni correction for multiple testing were evaluated. A two-sided *P*-value less than 0.05 was considered statistically significant. Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, United States) and Graphpad Prism version 8 software (La Jolla, CA, United States).

RESULTS

Demographic and clinical characteristics of SoJIA patients and HS

The total cohort comprised 64 children. The SoJIA group included 17 active and 15 inactive children, aged from 6 to 16 years, who were consecutively recruited into the study. The control group comprised 32 children aged from 5 to 16 years. No significant differences in age or gender were observed among the three groups. SoJIA patients received treatment with steroids/disease-modifying anti-rheumatic drugs (DMARDs)/biologics (Tocilizumab or Infliximab) in different combinations. Demographic and clinical characteristics at the time of sample collection are presented in Table 1 (more details in Supplementary Table S1).

A total of 5270328 effective tags were obtained by high-throughput sequencing from 64 specimens obtained from SoJIA patients and control subjects. The average number of effective tags per sample was 82349 (SoJIA: 82875; HS: 81823). Each effective tag had $Q_{20} > 98\%$ and $Q_{30} > 97\%$. Among all samples, tags with a similarly level of 97% were clustered into 2216 OTUs. Through annotation of the sequence of the OTUs with the Silva132 database, a total of 1097 (49.5%) OTU notes to the genus level were performed.

Microbiota profile in the two SoJIA groups versus the HS group

To characterize bacterial richness, rarefaction analysis was performed (Supplementary Figure S1). The curve in each group was near saturation, indicating sufficient sampling of the microbial communities. In order to evaluate differences in microbial biodiversity (alpha-diversity) among the three groups, we calculated the observed species, Chao1, Shannon, and Simpson indices. The results indicated that there were significant differences among the three groups in terms of observed species; the number of observed species was highest in the Active-SoJIA group, followed by the Inactive-SoJIA group, and then the HS group (Active-SoJIA *vs* HS: $P = 0.000$; Inactive-SoJIA *vs* HS: $P = 0.005$; Figure 1). The Chao1 index in both the Active-SoJIA and Inactive-SoJIA groups was significantly increased compared to the HS group (Active-SoJIA *vs* HS: $P = 0.000$; Inactive-SoJIA *vs* HS: $P = 0.006$; Supplementary Table S2 and Figure 1). This indicates that there was an increased richness in the microbiota of SoJIA patients. Assessment of the Shannon and Simpson indices showed no remarkable differences among the three groups (Figure 1). The significance of the alpha-diversity differences was calculated using the Kruskal-Wallis test with Bonferroni correction (*P*-value).

To estimate the between-sample (beta-diversity) variability in microbial communities, we calculated the Bray-Curtis and unweighted UniFrac dissimilarities.

Table 1 Clinical characteristics of systemic-onset juvenile idiopathic arthritis patients and healthy subjects

	A-SoJIA	Ina-SoJIA	HS	P-value
Number	17	15	32	-
Age, mean \pm SD, yr	10.9 \pm 3.3	11.7 \pm 2.8	10.3 \pm 2.9	NS ¹
Age range	6 to 15	7.3 to 16	5-16	-
Male, <i>n</i> (%)	9 (52.9)	7 (46.7)	18 (56.3)	NS ²
Disease duration, mean \pm SD, mo	58.4 (46.9)	48.5 (28)	-	NS ³
ESR (mm/h)	33 \pm 38	4 \pm 4	-	<i>P</i> < 0.01 ³
CRP (mg/L)	13.5 \pm 58.5	1 \pm 3	-	<i>P</i> < 0.01 ³

The *P*-values were calculated according to

¹ANOVA,

²Pearson chi-square test, and

³Mann-Whitney *U* test. SoJIA: Systemic-onset juvenile idiopathic arthritis; A-SoJIA: Active SoJIA, Ina-SoJIA: Inactive SoJIA; HS: Healthy subjects; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NS: Not significant.

PCoA on unweighted UniFrac and Bray-Curtis dissimilarities showed that both SoJIA samples (active and inactive) were more similar to each other than to the HS sample. PERMANOVA confirmed the differences among samples: Active-SoJIA *vs* HS (*P* = 0.001) and Inactive-SoJIA *vs* HS (*P* = 0.001); there was no significant difference between Active-SoJIA and Inactive-SoJIA (Figure 2A and 2B).

At the phylum level, Firmicutes and Bacteroidetes were the two most abundant phyla among the whole sample of both SoJIA children and controls (Supplementary Figure S2). The abundance of Firmicutes was lowest in Active-SoJIA, followed by Inactive-SoJIA, and was highest in HS (62.6% in Active-SoJIA, 64.7% in Inactive-SoJIA, and 71.0% in HS; Figure 3A and B). In contrast, the abundance of Bacteroidetes was highest in Active-SoJIA and lowest in HS (20.4% in Active-SoJIA, 16.3% in Inactive-SoJIA, and 14.8% in HS; Figure 3A and 3B). We then computed the Firmicutes/Bacteroidetes ratio for the three groups. A Firmicutes/Bacteroidetes ratio gradient from lowest (Active-SoJIA) to higher (Inactive-SoJIA) to highest (HS) was observed, though the only significant difference was noted between Active-SoJIA and HS (3.28 \pm 4.47 in Active-SoJIA, 5.36 \pm 8.39 in Inactive-SoJIA, and 5.67 \pm 3.92 in HS; Active-SoJIA *vs* HS: *P* = 0.048; Figure 3C). The decreased Firmicutes/Bacteroidetes ratio in SoJIA is similar to previous findings^[6]. The abundance of Erysipelotrichia and Erysipelotrichales in both active and inactive SoJIA populations was significantly decreased compared to HS (Active-SoJIA *vs* HS: *P* = 0.000; Inactive-SoJIA *vs* HS: *P* = 0.004; Figure 3). Family Ruminococcaceae was less abundant in Active-SoJIA compared with HS (14.9% in Active-SoJIA, 17.3% in Inactive-SoJIA, and 22.8% in HS; Active-SoJIA *vs* HS: *P* = 0.005; Figure 3). The abundance of Bacteroidaceae and Bacteroides was as follows: Active-SoJIA > Inactive-SoJIA > HS; there was a statistically significant difference between Active-SoJIA *vs* HS (16.5% in Active-SoJIA, 12.8% in Inactive-SoJIA, and 9.7% in HS; Active-SoJIA *vs* HS: *P* = 0.03; Figure 3). We observed a statistically significant predominance of Faecalibacterium in HS compared with Active-SoJIA (5.1% in Active-SoJIA, 9.9% in Inactive-SoJIA, and 13.0% in HS; Active-SoJIA *vs* HS *P* = 0.000; Figure 3). It is worth mentioning that most bacteria described above in the Inactive-SoJIA group showed a moderate abundance in the Active-SoJIA group and the HS group. Differential abundances of bacterial communities between Active-SoJIA, Inactive-SoJIA, and HS were tested by the Kruskal Wallis test; *P*-values were submitted to Bonferroni correction for multiple testing.

Associations between microbiota profile and clinical features in SoJIA patients

In order to determine whether microbiota composition is associated with clinical parameters in SoJIA patients, we performed Spearman rank correlations between clinical parameters and microorganisms at the phylum, family, and genus levels.

The Spearman correlation analyses revealed a direct association between patient age and phylum Chloroflexi. Disease duration was positively associated with family Burkholderiaceae, and negatively associated with genus Alistipes. CRP showed a positive association with Rhizobiaceae, and negative associations with Proteobacteria and Enterobacteriaceae. ESR was positively associated with Sellimonas and negatively correlated to Proteobacteria and Enterobacteriaceae. JADAS was positively correlated with Eggerthellaceae and Muribaculaceae, while Proteobacteria, Enterobacteriaceae,

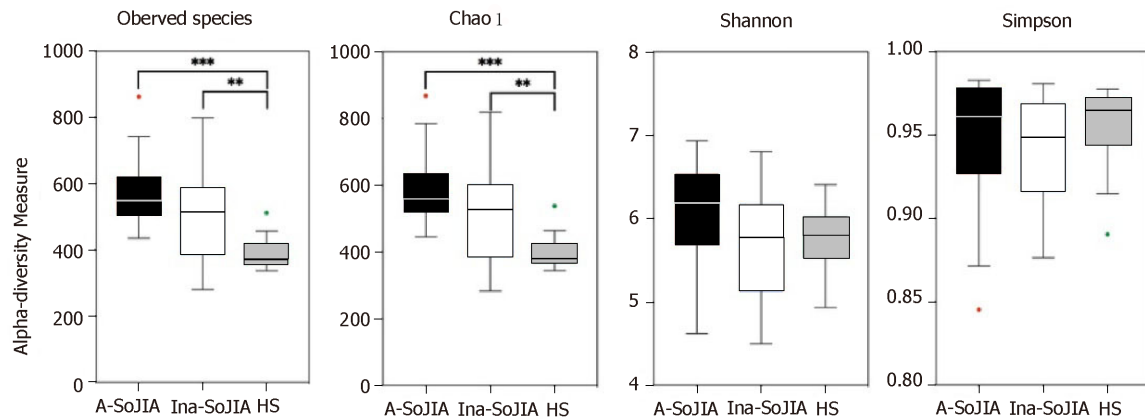


Figure 1 Box plots of observed species, Chao1 index, and Shannon and Simpson indices of microbiota for healthy subjects and systemic-onset juvenile idiopathic arthritis patients with different disease activities. Medians and interquartile ranges are shown. The significance of differences was calculated using the Kruskal-Wallis test with Bonferroni correction. ^a $P < 0.001$, A-SoJIA vs HS in observed species; ^b $P < 0.01$, Ina-SoJIA vs HS in observed species; ^c $P < 0.001$, A-SoJIA vs HS in Chao1; ^d $P < 0.01$, Ina-SoJIA vs HS in Chao1. SoJIA: Systemic-onset juvenile idiopathic arthritis; A-SoJIA: Active-SoJIA; Ina-SoJIA: Inactive-SoJIA; HS: Healthy subjects.

and *Faecalibacterium* were negatively correlated with JADAS (Supplementary Figure S3 and Figure 4).

DISCUSSION

This is the first report on the microbiota composition in SoJIA children. In our study, we applied 16S rDNA sequence analysis to characterize the intestinal microbiota of patients with SoJIA, taking into account the activity state of SoJIA disease. Our results confirmed that the composition of the intestinal microbiota is different in SoJIA patients compared to healthy children. In contrast to previous studies which have shown decreased microbiota richness or did not find any differences between JIA patients and control children^[17,18], our results showed that observed species and Chao1 index were highest in Active-SoJIA patients, followed by Inactive-SoJIA patients, and were lowest in healthy children. These findings indicate that there was an increase in microbiota richness in SoJIA patients, and the richness appeared to be decreased in patients who had achieved inactivity status. No significant differences in Shannon and Simpson indices were observed among the three groups. Measures of beta-diversity showed that both SoJIA samples (active and inactive) were more similar to each other than to the control group.

At the phylum level, compared to control children, the Active-SoJIA patients showed a lower abundance of Firmicutes and a higher abundance of Bacteroidetes. The low ratio of Firmicutes compared to the Bacteroidetes phylum in SoJIA is in accordance with another recent study in new-onset JIA patients (mainly oligoarticular or polyarticular) who were not treated with corticosteroids and DMARDs^[19]. In the United States and Asia, researchers have also observed an abundance in family Bacteroidaceae and genus *Bacteroides* in ERA patients^[17,19]. In addition, we computed the Firmicutes/Bacteroidetes ratio in the three groups, and a gradient from lowest (Active-SoJIA) to higher (Inactive-SoJIA) to highest (HS) was observed. Studies of patients with systemic lupus erythematosus (SLE) and type 1 diabetes have also shown a low Firmicutes/Bacteroidetes ratio^[9,20,21].

Bacteroides are primarily commensal organisms in the gut. Multiple species, including *B. fragilis* in the *Bacteroides* genus, can degrade mucin, an important component of the primary mucosal defense, leading to increased gut permeability^[22]. Agglutinins and histolytic enzymes of *B. fragilis* help bacteria adhere to the host mucosa, increasing the chance of bacteria entering the gut immune system, and thereby promoting the inflammatory process. In animal models of arthritis in germ-free conditions, articular inflammation can be activated by the introduction of *Bacteroides* spp., especially *B. vulgatus* and *B. fragilis*^[24]. Increased intestinal permeability has been identified both in children with JIA and in adults with ankylosing spondylitis^[25,26].

The decreased abundance of *Faecalibacterium* found in our analysis is in agreement with previous studies on polyarticular JIA and ERA^[17,27]. As butyrate-producing

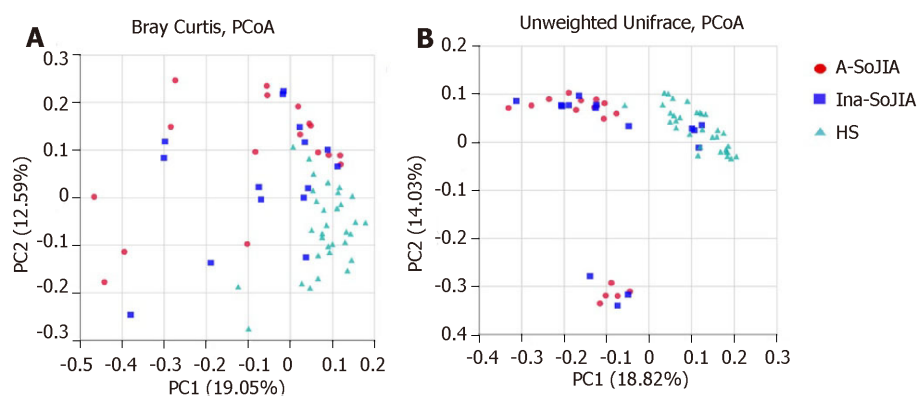


Figure 2 Principal coordinate analysis based on the overall structure of the stool microbiota in all samples. A: Principal coordinate analysis (PCoA) of Bray-Curtis dissimilarities; B: PCoA of unweighted UniFrac dissimilarities. Each data point represents an individual sample. Red: Active-SoJIA; Blue: Inactive-SoJIA; Green: Healthy subject samples.

bacteria, *Faecalibacterium* helps in maintaining the integrity and health of the gut epithelial barrier, and is considered to be an anti-inflammatory microorganism^[28-30]. Thus, a reduction in *Faecalibacterium* may induce an inflammatory status. When compared to healthy children, we found a statistically significant reduction in *Ruminococcaceae* in both SoJIA groups; this is similar to previous findings in oligoarticular and polyarticular JIA^[18]. In contrast to our results, two previous studies of JIA have shown depletion of *Ruminococcaceae*^[27,31]. Several factors can explain the partial inconsistency between our findings and other studies, such as different cohort size, JIA categories, and disease status, as well as different geographical, environmental, or dietary habits.

Another important finding of our study is that the Firmicutes/Bacteroidetes ratio and other bacterial alterations in the Inactive-SoJIA group were at a moderate level in the Active-SoJIA group and healthy children. This implies that the perturbed microbiota present in the Active-SoJIA group demonstrated partial restoration towards normal in inactive status patients. This result is consistent with a previous study. In 2016, Berntson *et al*^[16] described a child with polyarticular JIA refractory to multiple medicines, yet the girl showed remarkable clinical improvement accompanied by an elevation in Firmicutes/Bacteroidetes ratio during exclusive enteral nutrition treatment. Thus, we suspect that a low Firmicutes/Bacteroidetes ratio may be related to SoJIA activity status, and differences in microbial composition associated with disease activity may be useful as markers for disease monitoring.

In order to determine whether the microbiota composition is associated with clinical parameters in SoJIA patients, we performed correlation analyses between microorganisms and clinical parameters. Among the most remarkable results, Proteobacteria and Enterobacteriaceae displayed negative correlations with disease activity (JADAS-27), ESR, and CRP. The function of these microorganisms in humans requires further exploration.

Two registry-based case-control studies have suggested a significant association between early life antibiotic use and subsequent JIA; the relationship was dose-dependent and the more antibiotic categories that were used, the higher the risk. This suggests that the greater the overall perturbation in the microbiota, the greater the risk of JIA^[28,32,33]. A study of children at risk for type 1 diabetes showed that changes in gut microbiota composition and diversity preceded the development of the clinical disease^[34]. Another study of hypertension showed that compared with healthy people, the microbiome characteristics of individuals with pre-hypertension were quite similar to those of individuals with hypertension, indicating that gut dysbiosis had already occurred in the pre-hypertension stage^[35]. Zhang *et al*^[7] reported that dysbiosis had been partially restored to normality in rheumatoid arthritis patients showing clinical improvement after prescription of disease modifying antirheumatic drugs. Our data showed that an improvement in clinical symptoms after treatment was associated with partial reversal of the disease-related dysbiosis. Taken together, the above findings suggest that the intestinal microbiota plays a crucial role in disease promotion and clinical course, and that maintaining the homeostasis of intestinal flora is essential for the host's health.

Diet is one of the main factors contributing to the modulation of gut microbiota composition. Previous studies have reported that the balance of Bacteroidetes and Firmicutes can be modified by dietary patterns^[36,37]. Therefore, we speculate that diet,

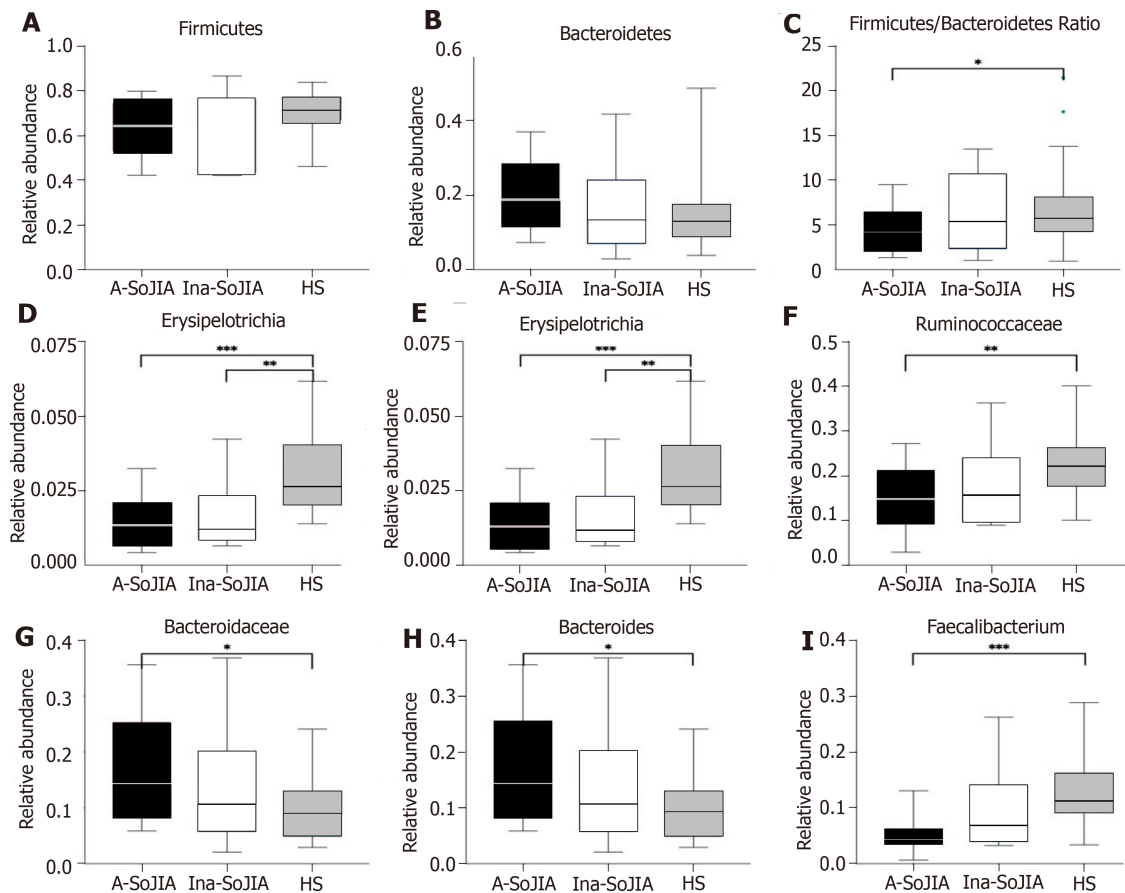


Figure 3 Relative abundances of fecal bacterial components in systemic-onset juvenile idiopathic arthritis and healthy subjects groups. A: Box plots of Firmicutes; B: Box plots of Bacteroidetes; C: Box plots of Firmicutes/Bacteroidetes ratio; D-I: Box plots of statistically significantly different bacteria at levels below phylum. Significance was calculated by the Kruskal-Wallis test with Bonferroni correction.

which affects the microbiota composition, can in turn influence these disorders. Modifications to the microbiota through dietary interventions could be a new approach to preventing and managing SoJIA.

There were several strengths of our study. First, we studied SoJIA patients with differing disease activity states and compared these to healthy controls. We also conducted regular follow-up of patients, as the clinical manifestations of SoJIA may be similar to the early manifestations of other diseases, such as tumors. The shortest follow-up period in this study was 10 months, and the patient was in a good state following treatment.

A limitation of our study was that our patients were not new-onset SoJIA patients and had received treatment for arthritis or systemic symptoms with DMARDs/steroids/biologics in different combinations prior to sample collection. This could have had an effect on gut microbiota. However, it is difficult to obviate this limitation in this disease. Due to the wide variation in signs and symptoms, the diagnosis of SoJIA at disease onset is challenging and diagnosis is usually made through exclusion. Infectious agents are considered to be one of potential environmental triggers of SoJIA pathogenesis; thus, antibiotics are often used at disease onset of SoJIA. Numerous studies have shown that antibiotics have an effect on the contents of the microbiota. Thus, in order to reduce the interference associated with the effects of antibiotic use on intestinal microbiota, we excluded new-onset patients who had used antibiotics within one month before enrollment. The small sample was another limitation, and is a result of the rarity of SoJIA. Therefore, further studies are required to draw comprehensive conclusions in the future.

In summary, our results demonstrated that the composition of the intestinal microbiota is different in SoJIA patients compared to healthy children. The perturbed microbiota demonstrated partial restoration in inactive status patients after treatment.

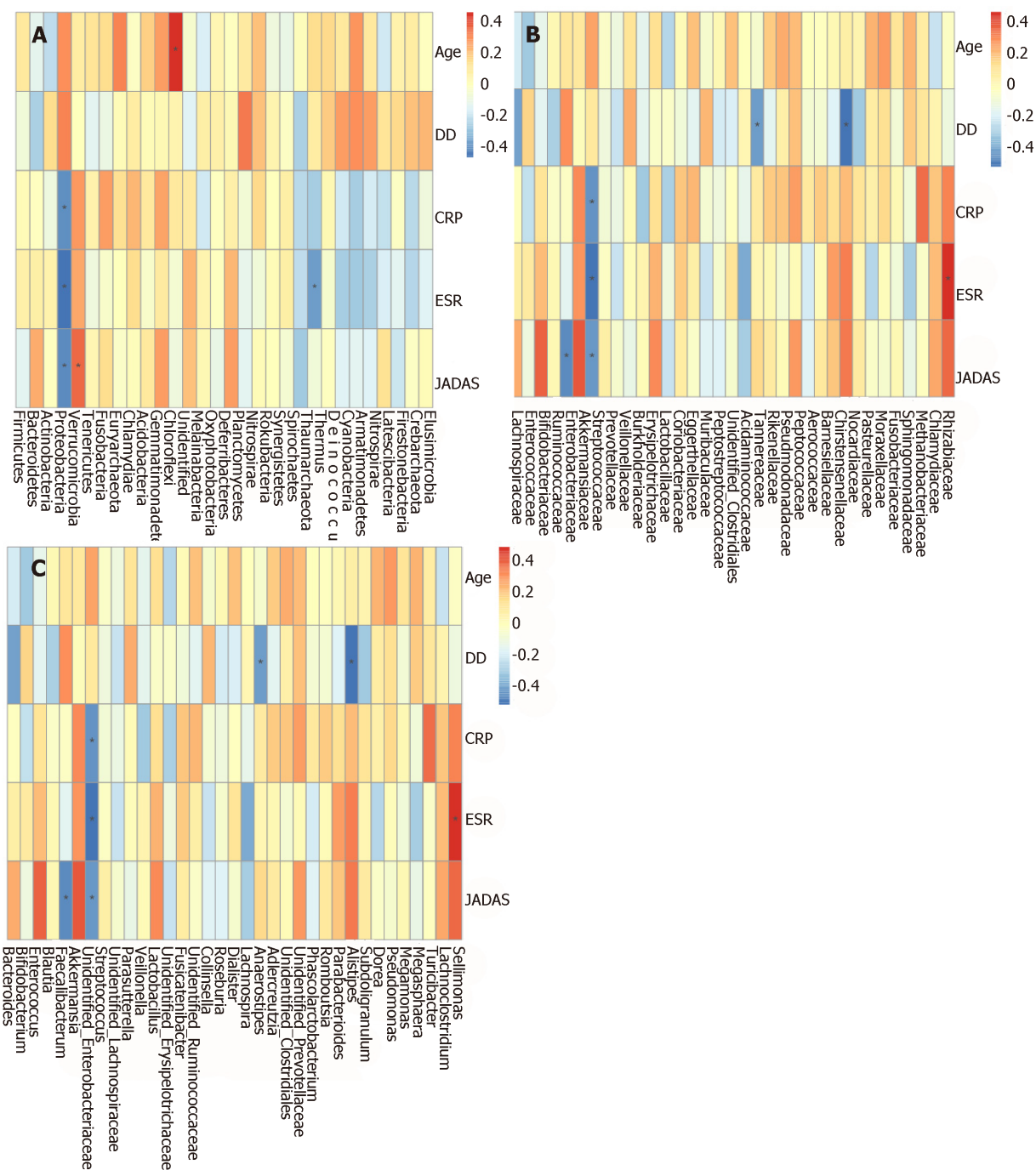


Figure 4 Associations between gut microbiota profile and clinicopathological features in systemic-onset juvenile idiopathic arthritis patients at the (A) phylum, (B) family, and (C) genus levels. DD: Disease duration; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; JADAS: Juvenile arthritis disease activity score.

ARTICLE HIGHLIGHTS

Research background

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a serious chronic rheumatic disease of childhood. The pathogenesis of SoJIA remains unclear, and several studies suggest that perturbation of gut microbiota, dysbiosis, could contribute to development of JIA. Understanding the intestinal microbial characteristics may contribute to the prevention and treatment of SoJIA.

Research motivation

Research motivation

We aimed to characterize the gut microbiota in SoJIA and to analyze the changing trend of intestinal flora as the disease improved.

Research objectives

Our main purpose was to characterize the gut microbiota in SoJIA and investigate the correlation between the abundance of intestinal microorganisms and clinical indicators as well as the pathogenesis of SoJIA from the perspective of microorganisms.

Research methods

We carried out an observational single-center study. A total of 32 patients and 32 healthy children were enrolled. The patients were divided into two groups: Active-SoJIA and Inactive-SoJIA. Clinical data and stool samples were collected from SoJIA patients when they visited the hospital.

Research results

Alpha-diversity analysis indicated that there was an increased richness in the microbiota of SoJIA patients. Measures of beta-diversity showed that characteristics of gut microbiota of both SoJIA samples (active and inactive) were more similar to each other than to the control group. The Firmicutes/Bacteroidetes ratio and the abundance of Erysipelotrichales, Ruminococcaceae, and Faecalibacterium were decreased in SoJIA. By contrast, the abundance of Bacteroides and Bacteroidaceae was increased in SoJIA. The Firmicutes/Bacteroidetes ratio and other bacterial abundance in the Inactive-SoJIA group were at a moderate level between the Active-SoJIA group and healthy children. Proteobacteria and Enterobacteriaceae were negatively correlated with disease activity.

Research conclusions

The composition of the intestinal microbiota is different in SoJIA patients compared to healthy children. The perturbed microbiota demonstrated partial restoration in inactive status patients after treatment.

Research perspectives

There are many factors affecting gut microbiota composition. Future studies should prospectively collect multicenter data on new-onset SoJIA patients, and analyze the changing trend of intestinal flora of each patient as the disease improves to eliminate the interference of geographical, environmental, or dietary habits on intestinal flora.

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