



Compositional changes in fecal microbiota associated with clinical phenotypes and prognosis in Korean patients with inflammatory bowel disease

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Background/Aims: The fecal microbiota of Korean patients with inflammatory bowel disease (IBD) was investigated with respect to disease phenotypes and taxonomic biomarkers for diagnosis and prognosis of IBD. **Methods:** Fecal samples from 70 ulcerative colitis (UC) patients, 39 Crohn's disease (CD) patients, and 100 healthy control individuals (HC) were collected. The fecal samples were amplified via polymerase chain reaction and sequenced using Illumina MiSeq. The relationships between fecal bacteria and clinical phenotypes were analyzed using the EzBioCloud database and 16S microbiome pipeline. **Results:** The alpha-diversity of fecal bacteria was significantly lower in UC and CD ($P < 0.05$) compared to that in HC. Bacterial community compositions in UC and CD were significantly different from that of HC according to Bray-Curtis dissimilarities, and there was also a difference between community composition in UC and CD ($P = 0.01$). In UC, alpha-diversity was further decreased when the disease was more severe and the extent of disease was greater, and community composition significantly differed depending on the extent of the disease. We identified 9 biomarkers of severity and 6 biomarkers of the extent of UC. We also identified 5 biomarkers of active disease and 3 biomarkers of ileocolonic involvement in CD. *Lachnospiraceae* and *Ruminococcus gnavus* were biomarkers for better prognosis in CD. **Conclusions:** The fecal microbiota profiles of IBD patients were different from those of HC, and several bacterial taxa may be used as biomarkers to determine disease phenotypes and prognosis. These data may also help discover new therapeutic targets for IBD. (Intest Res 2023;21:148-160)

Key Words: Inflammatory bowel disease; Microbiota; Biomarkers; Phenotype; Prognosis

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INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disorder of the intestinal tract characterized by relapsing abdominal pain, diarrhea, and hematochezia.¹⁻³ Because IBD patients experience periods of various clinical courses according to the degree of inflammation, the optimal treatment of IBD should be applied according to the severity and extent of the

disease.^{4,5} As a result, the main challenge most clinicians face is identifying the disease phenotype before therapeutic assessment. Determination of the disease phenotype and prognosis could help to overcome the current situation in which many IBD patients experience disease complications. Several parameters based on laboratory tests and endoscopic findings have been suggested and are used for prognosis^{6,7}; however, they are invasive and have unsatisfactory predictability. More dependable biomarkers are, thus, required.

In recent years, with the development of genome sequencing methods, the role of gut microbiota has been highlighted in the pathogenesis of IBD. The gut microbiota represents a complex and dynamic microbial ecosystem in the human colon,⁸ and developing evidence has demonstrated that there is a distinct shift in composition of gut microbiota in IBD patients compared with healthy control individuals (HC). A lower richness and diversity of microbial species are commonly identified in IBD patients.^{9,10} Compositional changes in bacterial communities have also been found from the phylum to the species level.^{9,11} Recently, it has been hypothesized that specific microbial pathways control intestinal barrier function and that a dysbiosis-induced inflammatory cascade drives disease development.¹²⁻¹⁷ Even the clinical outcomes of anti-tumor necrosis factor (TNF) therapy are suggested to be related to the intestinal microbiota.¹³

Host-microbiota interactions provide new insights for disease assessment and treatment in IBD. However, the diagnostic and prognostic role of microbiota in IBD patients remains unclear to date. Given the entity of IBD, which presents various disease phenotypes, clinical studies have been needed to discover biomarkers associated with the disease status and course. Identifying the characteristic gut microbiota associated with the disease phenotype and prediction of clinical courses may contribute to not only the growing area of these fields of research, but also optimal treatment for IBD patients. Thus, the aim of this study was to investigate the fecal microbiota of IBD patients and their relationship to disease phenotypes. We further explored taxonomic biomarkers associated with prognosis in Korean patients with IBD.

METHODS

1. Participants and Baseline Assessment

This study involved 3 academic hospitals in Korea. The study protocol was approved by an institutional review board at each center including Chung-Ang University Hospital (IRB No.

C2013183[1143]). All participants voluntarily agreed to participate in this study and gave written informed consent. A baseline assessment was performed before fecal sampling, and demographic information including age, sex, and body mass index (BMI) were collected. Patients who used drugs can affect intestinal microbial community, such as probiotics and antibiotics, within a month were excluded. Prior exposure to azathioprine/6-mercaptopurine and anti-TNF- α agents was evaluated for each participant. Previous history of disease-related operations included small bowel resection, ileocelectomy and anal fistulectomy.

The disease extensions of UC were defined as proctitis, left sided colitis, and extensive colitis, and those of CD were ileal, colonic, and ileocolonic. The severity of disease was assessed by the Mayo score¹⁸ for UC (3–5, mild; 6–10, moderate; 11–12, severe) and the Crohn's Disease Activity Index¹⁹ for CD (<150, remission; 150–219, mild; 220–449, moderate; >450, severe). Severity was estimated at the time of fecal sampling, and the average follow-up period was 8.0 ± 1.3 years. Patients with UC and CD were divided into 2 groups based on clinical courses. A “worse prognosis group” was defined as patients who experienced biologic agents (including anti-TNF- α agents) or surgical treatment after fecal sampling. A “better prognosis group” was defined as patients who did not experience such treatments. Fecal samples of HC were collected from participants of the local community cohort studies which had conducted in the Department of Preventive Medicine, Ewha Womans University College of Medicine. Stool samples were obtained from participants without underlying disease and abdominal symptoms.

2. Fecal Sample Collection and Analysis

Fecal samples were collected between January 2009 and December 2012, and DNA was isolated from feces and stored at -80°C . DNA was extracted using a FastDNA SPIN kit for bacterial DNA (MP Biomedicals, Santa Ana, CA, USA) according to the manufacturer's instructions. In this study, the bacterial portion of the DNA samples were characterized by amplification of the V4 variable region of the 16S rRNA gene by polymerase chain reaction (PCR) (forward primer 5'-GAGTGCCAGCMGCCGCGGTAA-3'; reverse primer 5'-ACGGACTACHVGGGTWTCTAAT-3'). The forward and reverse primers use single nucleotide shifts of 6 different lengths to improve sequence quality. Two steps of amplification were run on the DNA samples (Supplementary Material). After each PCR reaction, products were cleaned using the HighPrep PCR clean-up kit

with a DynaMag-96 side magnet. Cleaned 16S PCR products were then quantified and pooled at equimolar concentrations for sequencing. The quality and product size were assessed on a Bioanalyzer 2100 (Agilent, Palo Alto, CA, USA) using a DNA 7500 chip. Mixed amplicons were pooled and sequencing was carried out by the High-Throughput Sequencing Facility at the University of North Carolina at Chapel Hill School of Medicine.

3. Data Processing and Statistical Analysis

Once taxonomic or functional profiles of samples were generated, we used a web-based analysis platform for a secondary analysis with versatile visualizations and statistical reports. The EzBioCloud 16S database and 16S microbiome pipeline (EzBioCloud 16S-based MTP app, <https://www.EZbiocloud.net>; ChunLab Inc., Seoul, Korea) were used for data processing, statistical analysis, and data graphing.

The information collected in the pipeline was analyzed using various statistical tools. Species richness indices were de-

termined using the Wilcoxon rank-sum test. The Chao1 estimation and Shannon diversity index were used for the richness and evenness of samples. Permutational multivariate analysis of variance based on Bray-Curtis dissimilarities at the operational taxonomic unit level was used to determine differences in bacterial communities among groups. Biomarkers were determined using linear discriminant analysis (LDA) with effect size estimation (LefSe) with an LDA effect size >3.0 to distinguish between (1) different disease groups, (2) disease severity and extent, and (3) prognosis groups.

RESULTS

1. Study Population

A total of 209 samples from 100 HC, 70 UC patients, and 39 CD patients were enrolled. Table 1 shows the baseline demographic and clinical characteristics of all participants. HC and UC patients had no difference in age and BMI, but the mean age and BMI were significantly lower in CD patients com-

Table 1. Baseline Demographic and Clinical Characteristics of All Participants

Characteristics	Healthy control individual (n = 100)	Ulcerative colitis patient (n = 70)	Crohn's disease patient (n = 39)
Age (yr), mean ± SD	44.1 ± 8.8	46.3 ± 14.4	35.3 ± 11.7
Male sex, No. (%)	54 (54.0)	44 (62.9)	30 (76.9)
BMI (kg/m ²), mean ± SD	23.0 ± 3.2	23.0 ± 2.8	20.7 ± 3.5
Disease extent (maximum), No. (%)			
Ulcerative colitis, No. (%)	-		-
Proctitis		21 (30.0)	
Left sided colon		28 (40.0)	
Extensive		21 (30.0)	
Crohn's disease, No. (%)	-	-	
Colon			5 (12.8)
Small bowel only			17 (43.6)
Ileocolon			17 (43.6)
Disease severity (maximum), No. (%)	-		
Mild		37 (52.8)	6 (15.4)
Moderate		16 (22.9)	6 (15.4)
Severe		2 (2.9)	3 (7.7)
Remission		15 (21.4)	24 (61.5)
Concomitant drug use, No. (%)	-		
5-ASA		70 (100)	-
Steroid		1 (1.4)	-
Azathioprine/6-MP		9 (12.9)	29 (74.3)
Biologic agent		1 (1.4)	4 (10.3)
Previous history of disease-related operations		0	14 (35.9)

SD, standard deviation; BMI, body mass index; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine.

pared to the 2 groups. One patient received biologic agents in UC and 10.3% of patients (4/39) experienced biologic agents in CD. In 35.9% of patients (14/39) had previous history of disease-related operations in CD.

2. Microbial Diversity and Composition in UC and CD

Patients

1) Microbial Diversity

Analysis of alpha diversity revealed that both richness and diversity were significantly lower in IBD patients compared with HC (Fig. 1A). The Shannon diversity index was significantly lower in UC and CD compared to HC, and significantly lower in CD compared with UC (Fig. 1B). Analysis using Bray-Curtis dissimilarities and principal co-ordinates analysis revealed significant differences in microbial communities among HC, UC, and CD (Fig. 1C).

In UC patients, alpha diversity decreased as the disease severity (Fig. 2A) and extent (Fig. 2B) deteriorated. There were

significantly distinct bacterial community compositions between patients with proctitis and left sided or extensive colitis (Supplementary Fig. 1). No significant differences in alpha diversity or community composition were identified according to disease severity and extent in CD patients.

2) Microbial Composition

Bacterial compositions of HC were different from those of IBD patients, especially for CD. Compared to HC and patients with UC, CD patients had significantly higher abundances of the phylum Proteobacteria (7.19% and 7.68% vs. 24.06%, $P < 0.001$) (Fig. 3A), the genus *Escherichia* (2.00% and 2.20% vs. 11.01%, $P < 0.001$) (Fig. 3B), and the species *Escherichia coli* (2.00% and 2.20% vs. 11.02%, $P < 0.001$) (Fig. 3C).

LefSe analysis identified 9 bacterial taxa (including the *Proteus vulgaris* group, the *Bifidobacterium dentium* group, the *Clostridium clostridioforme* group, and *Flavonifractor plautii*) that were significantly more abundant in UC patients than HC

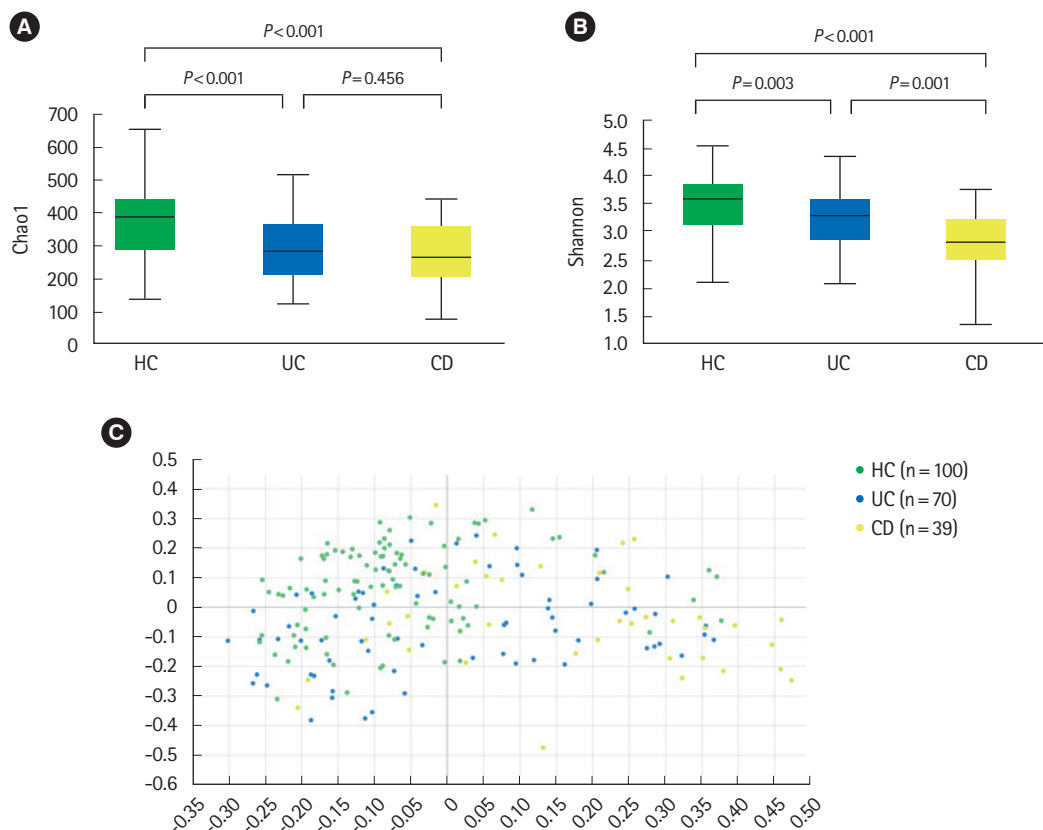


Fig. 1. Diversity of fecal microbiota in a HC, UC patients, and CD patients. (A) Chao 1 index, (B) Shannon index, and (C) beta diversity based on Bray-Curtis dissimilarities. Both richness and diversity were significantly lower in inflammatory bowel disease patients compared with HC, and Shannon diversity index was significantly lower in CD compared with UC. *Post hoc* analyses using pair-wise comparisons showed that 3 groups were significantly different from each other (HC vs. UC, $P = 0.001$; HC vs. CD, $P = 0.001$; UC vs. CD, $P = 0.001$). HC, healthy control individuals; UC, ulcerative colitis; CD, Crohn's disease.

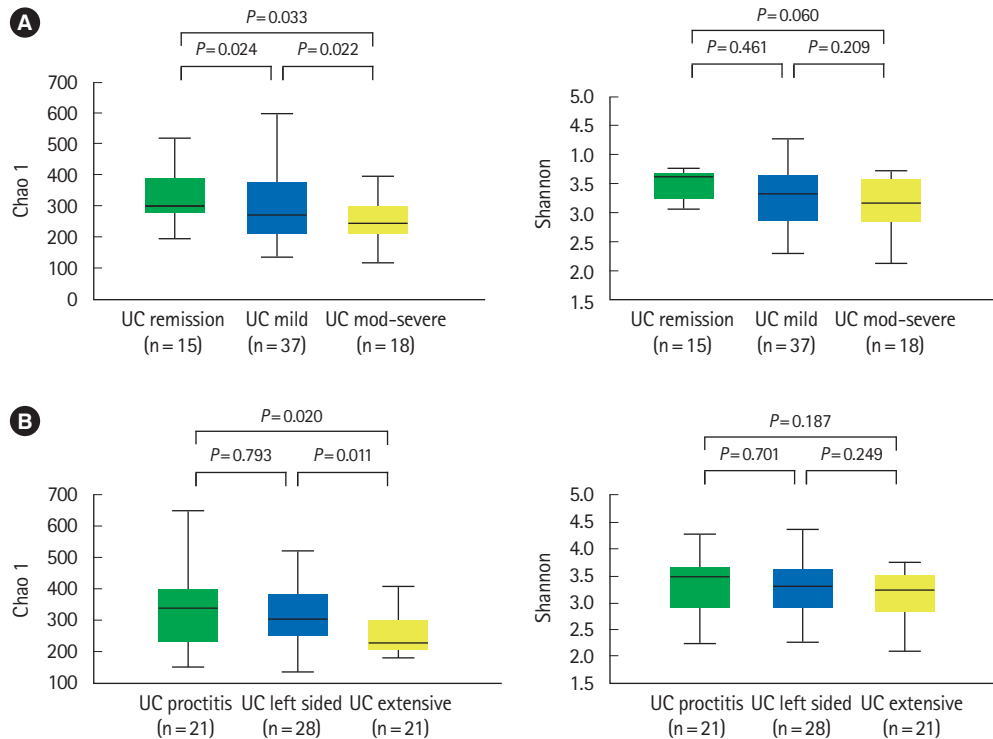


Fig. 2. Diversity of fecal microbiota in ulcerative colitis (UC) patients according to disease severity (A) and disease extent (B). Alpha diversity decreased as the disease severity and extent deteriorated.

(Fig. 4A), and 14 bacterial taxa (including the *Pseudomonas fragi* group, the *Lactobacillus gasseri* group, the *Streptococcus galloyticus* group, the *Bifidobacterium dentium* group, the *Veillonella parvula* group, and the *Lactococcus garvieae* group) that were significantly more abundant in CD patients than HC (Fig. 4B).

3. Taxonomic Biomarkers for Disease Severity and Extent

1) Ulcerative Colitis

Taxa that could differentiate 1 group from another, in terms of disease severity and extent, were determined using LefSe. The *Lactobacillus salivarius* group and *Clostridioides difficile* group were identified as potential biomarkers for moderate to severe UC, compared to mild UC (Fig. 5A). The *Lactobacillus lactis* group, *Intestinibacter bartlettii*, the *C. difficile* group, the *Weissella confusa* group, the *Anaerostipes hadrus* group, *Clostridium spiroforme*, the *Leuconostoc lactis* group, and the *Lactobacillus plantarum* group were identified as potential biomarkers for moderate to severe UC, compared to remission status (Fig. 5B). Several taxa were found to be associated with disease extent. *Bifidobacterium bifidum*, *I. bartlettii*, *F. plautii*, the *A. hadrus* group, the *Lactobacillus paracasei* group, and *Ruminococcus gnavus* were identified as potential biomarkers for

left sided or extensive colitis compared to proctitis (Fig. 5C).

2) Crohn's Disease

The *Phascolarctobacterium succinatutens* group, the *L. salivarius* group, *Lactobacillus mucosae*, the *Porphyromonas asaccharolytica* group, and *Coprococcus catus* were identified as possible biomarkers for active disease status, compared to remission status (Fig. 6A). The *L. gasseri* group, the *Bacteroides ovatus* group, and the *W. confusa* group were identified as possible biomarkers for ileocolonic involvement, compared to small bowel involvement only (Fig. 6B).

4. Taxonomic Biomarkers for Prognosis

Of the UC and CD patients, 13 and 9 belonged to worse prognosis group, respectively. In CD patients, *Lachnospiraceae* (Fig. 7A) and *R. gnavus* (Fig. 7B) were significantly more abundant in the better prognosis group compared to the worse prognosis group. We found no significantly different abundances among the better and worse prognosis groups in UC patients.

DISCUSSION

In the present study, we demonstrated the dysbiosis of fecal

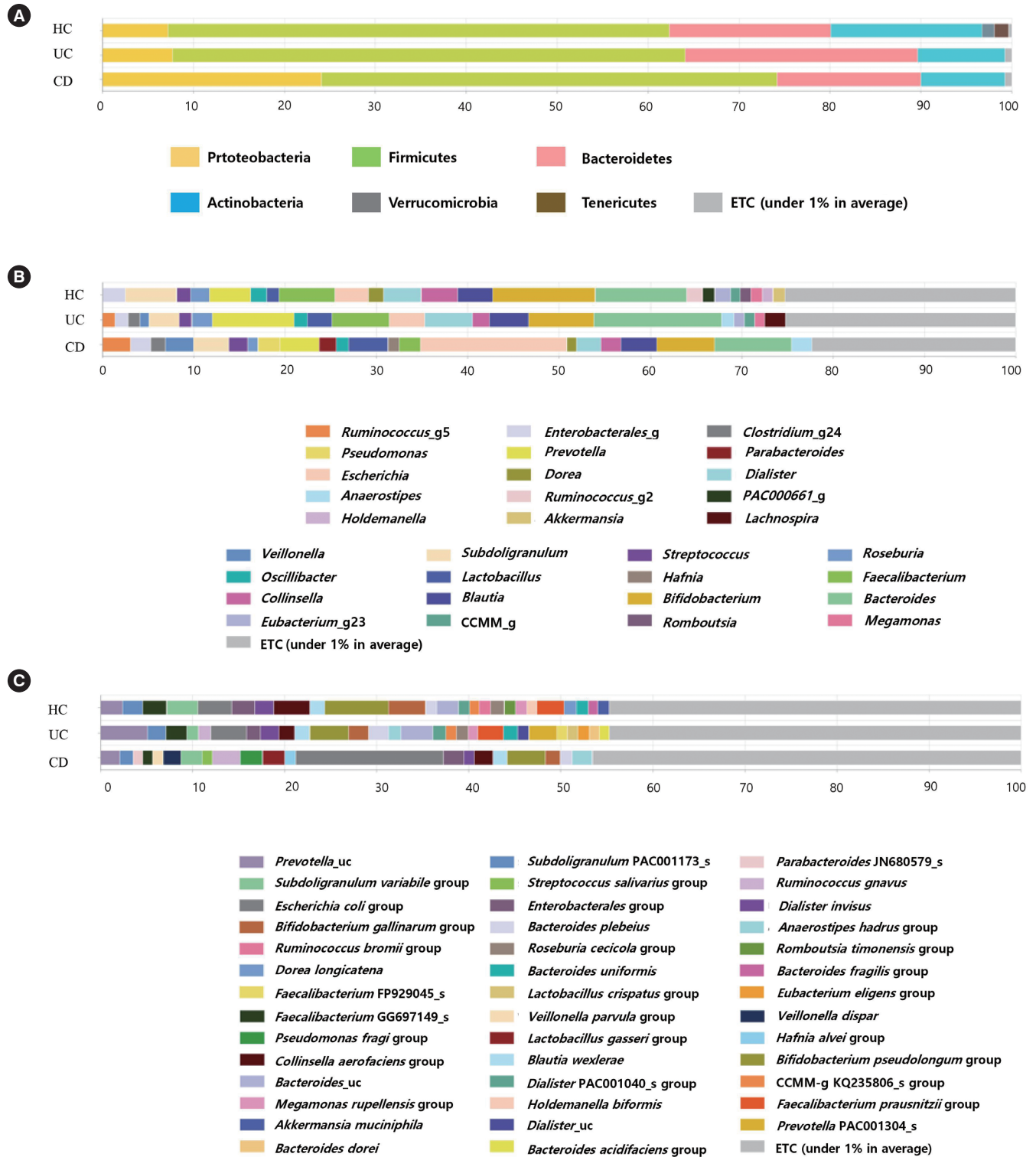


Fig. 3. Composition of fecal microbiota in HC, UC patients, and CD patients at the phylum (A), genus (B), and species (C) level. Compared to HC and UC patients, CD patients had significantly higher abundances of the phylum Proteobacteria, the genus *Escherichia*, and the species *Escherichia coli*. HC, healthy control individuals; UC, ulcerative colitis; CD, Crohn's disease.

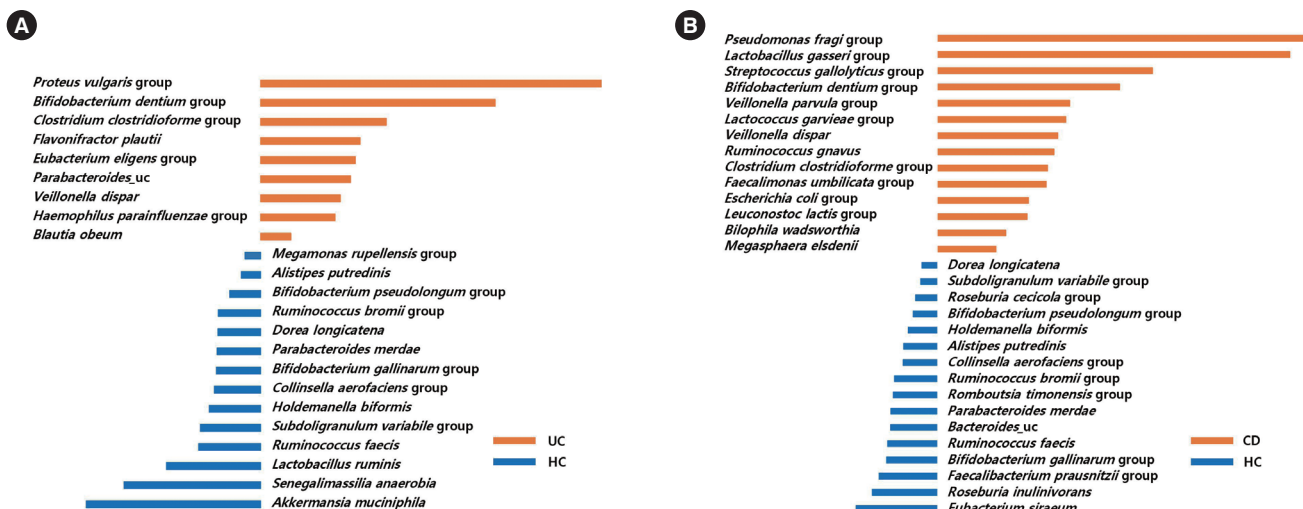


Fig. 4. Taxa list according to linear discriminant analysis values determined from comparisons between HC and UC patients (A), and between HC and CD patients (B). Effect size estimation analysis identified 9 bacterial taxa that were significantly more abundant in UC patients than HC (A), and 14 bacterial taxa that were significantly more abundant in CD patients than HC. HC, healthy control individuals; UC, ulcerative colitis; CD, Crohn's disease.

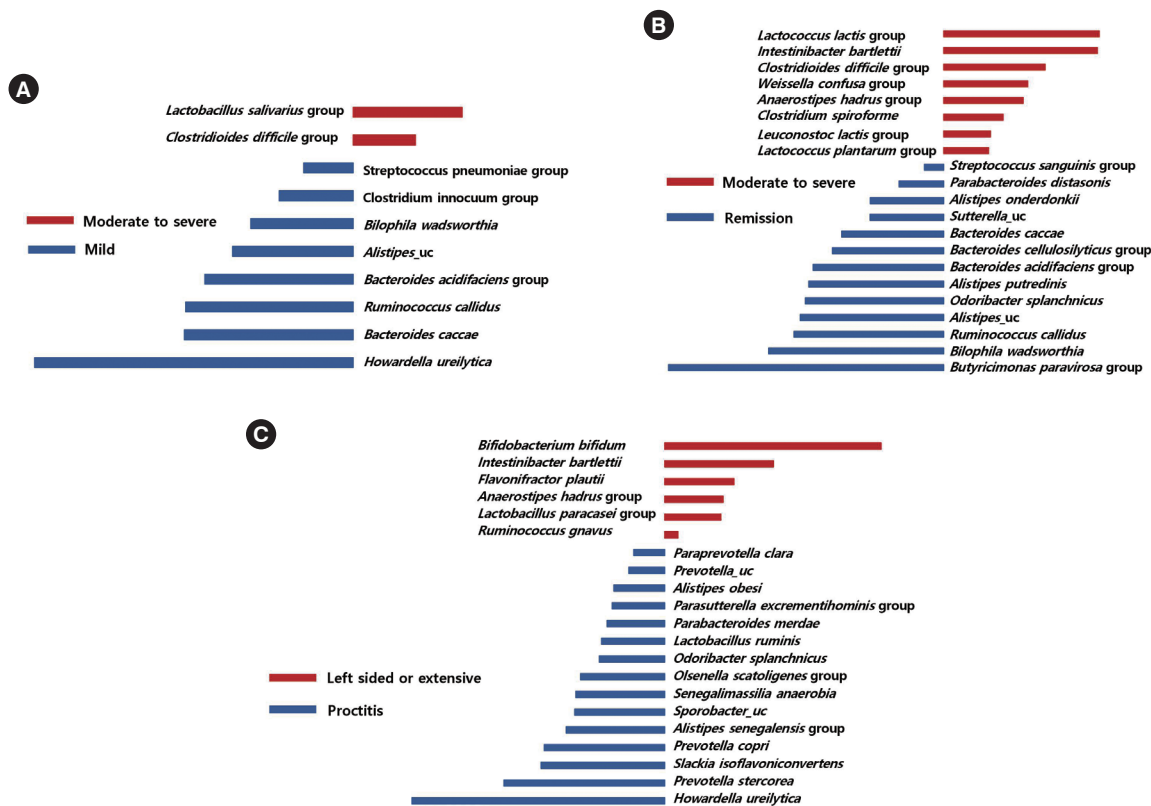


Fig. 5. Taxa list according to linear discriminant analysis values determined from comparisons according to disease severity and extent in ulcerative colitis (UC) patients. Comparisons between moderate to severe and mild UC (A), between moderate to severe UC and remission (B), and between left sided or extensive UC and proctitis (C). Some bacterial taxa (red color) were identified as potential biomarkers for moderate to severe UC compared to mild UC (A), and remission status (B). Several bacterial taxa (red color) were found to be associated with left sided or extensive UC (C).

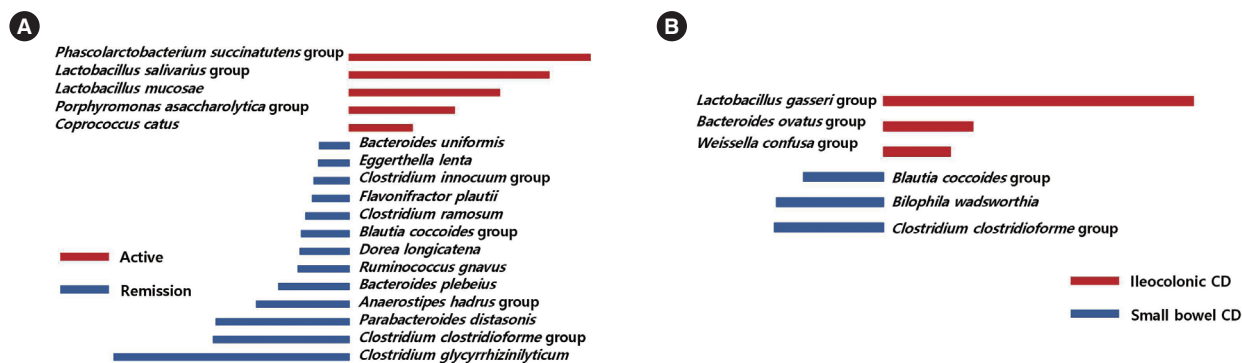


Fig. 6. Taxa list according to linear discriminant analysis values determined from comparisons according to disease severity and extent in Crohn's disease (CD) patients. Comparisons between remission and active CD (A) and between ileocolonic and small bowel CD (B). Some bacterial taxa (red color) were identified as possible biomarkers for active disease status, compared to remission status (A). Several bacterial taxa (red color) were identified as possible biomarkers for ileocolonic involvement, compared to small bowel involvement only (B).

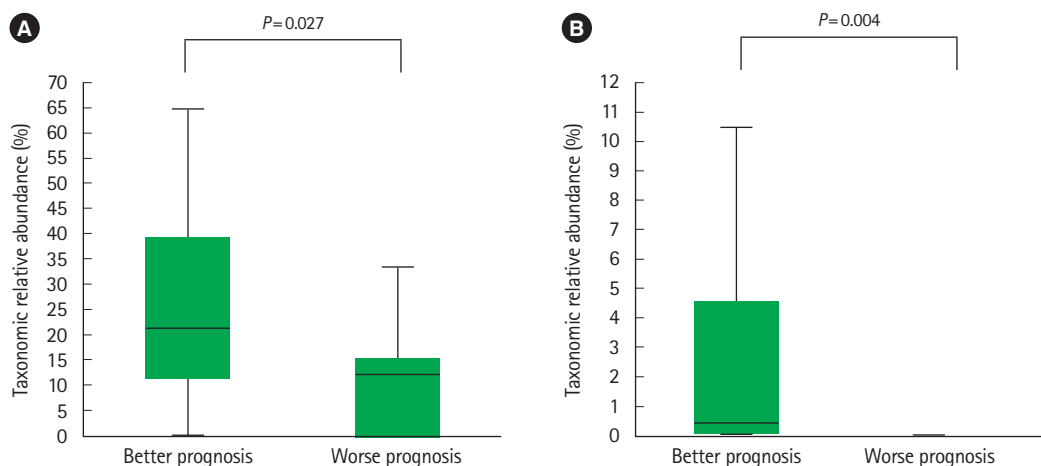


Fig. 7. Relative abundance of particular taxa in Crohn's disease (CD) patients based on prognosis. (A) *Lachnospiraceae* and (B) *Ruminococcus gnavus*. Better prognosis is defined as patients who did not consume biologic agents including anti-tumor necrosis factor (TNF)- α agents or surgical treatment after fecal sampling and worse prognosis is defined as patients who either were administered biologic agents including anti-TNF- α agents or required surgical treatment after fecal sampling ($n=9$). *Lachnospiraceae* and *R. gnavus* were significantly more abundant in the better prognosis group compared to the worse prognosis group.

microbiota in IBD patients. The alpha-diversity of the fecal microbiota was significantly lower in IBD patients compared to HC. Additionally, there were significant differences in bacterial community composition among UC and CD patients and HC. In UC patients, species richness decreased as the degree of severity and extent deteriorated, and distinct compositional differences were identified according to the disease extent. We also identified several microbial taxonomic biomarkers correlating to the disease severity and extent in UC and CD patients, which may be associated with prognosis of the diseases.

This study confirmed the findings of previous studies that

microbial diversity is significantly lower in IBD patients.^{11,20} Additionally, we found that compared to UC patients, the microbial diversity of CD patients was significantly lower. Previous studies have conflicting results regarding microbial differences between UC and CD patients.^{11,21,22} In the present study, the lower diversity in CD patients is assumed to be associated with compositional changes in the microbiota in CD. The phylum Proteobacteria, genus *Escherichia*, and species *E. coli* were significantly more abundant in CD patients compared to UC patients and HC. An increased abundance of Proteobacteria has commonly been identified in IBD patients,^{23,24} and previous studies have shown that this is more evident in patients

with aggressive CD. A higher abundance of *E. coli* in CD patients has also been reported in previous literature.^{25,26} Meanwhile, this was not observed in UC patients, which does not support previous studies showing a higher abundance of *E. coli* in UC patients, as well as CD.²⁷⁻³⁰ Further studies on the role of *E. coli* in UC are needed.

We found several microbial species with significantly different abundances in IBD patients compared to HC. Few previous studies have considered compositional changes in gut microbiota at the species level.^{11,12,25} However, *Faecalibacterium prausnitzii* and *R. gnavus* have previously been found to be associated with IBD.^{31,32} Further large-scale studies are needed to confirm the role of the species identified in this study in the pathogenesis of IBD.

In a Western cohort study, patients with active IBD had lower intestinal bacterial species richness and diversity compared with those with inactive disease status.²³ Moreover, the abundance of Firmicutes was lower in patients with active UC, and that of Proteobacteria was higher in patients with aggressive CD compared with patients with non-active and non-aggressive disease status, respectively. Pediatric patients with CD who had a higher abundance of Proteobacteria were more likely to have complicated disease behavior.³² A meta-analysis also showed a significantly lower abundance of potentially protective taxa, such as *F. prausnitzii* and *Bifidobacterium*, in patients with active IBD compared with those in remission status.³³ In the present study, we investigated bacterial taxa at the species level to determine differences related to the degree of disease severity and extent. Two species, *L. salivarius* and *C. difficile*, were identified as biomarkers to differentiate moderate to severe disease from mild disease in UC patients. *L. salivarius* was also a biomarker of active CD compared with a remission status. *L. salivarius* strains are used as probiotics; they have anti-inflammatory effects and improve intestinal permeability.^{34,35} However, their role in IBD has been controversial,³⁶ and even if the species are the same, the function of the bacteria can be significantly different if the strain is different. Therefore, *L. salivarius* presented in our study might be different strain from that of *L. salivarius* used as probiotics. Unfortunately, however, our study did not confirm their strains. Further studies for additional confirmation are needed. *Clostridioides*, which includes several pathogenic taxa including *C. difficile*, is a cause of colitis. It is not clear whether *C. difficile* initiates or deteriorates the inflammatory response in the intestine, but increasing evidence has shown that the incidence of *C. difficile* infection is higher in IBD patients,^{37,38} particularly in

UC patients.³⁹ *C. difficile* was also suggested as a cause of an IBD relapse in a previous retrospective study.⁴⁰ Our data showed that *C. difficile* is a biomarker that differentiates moderate to severe disease, not only from mild disease but also from remission status. However, more frequent exposure to antibiotics and other drugs (including immunomodulators) may be associated with a higher abundance of *C. difficile* in patients with moderate to severe UC.^{41,42}

Endoscopy plays an important role in the diagnosis and evaluation of disease status in IBD patients, particularly for the classification of the disease location. However, endoscopies are invasive and cause discomfort in patients; therefore, physicians hesitate to perform this procedure frequently. Noninvasive detection tools are required. Several serologic markers and imaging-based modalities have been investigated, but their role in assessing disease location is limited.^{43,44} Assessment using intestinal microbiota has also been suggested; however, data has been limited and conflicting. One study using cohort data showed no differences in diversity or phyla-level abundance in relation to disease location.²³ However, another study showed that patients with ileocolic CD and extensive UC had higher abundances of *R. gnavus* compared with patients with isolated CD and UC limited to left side or proctitis, respectively.³² They also showed that *Veillonella* is more abundant in patients with upper gastrointestinal CD. In the present study, *B. bifidum* was a biomarker for left sided or extensive UC compared with proctitis. Previous results regarding the abundance of *Bifidobacterium* in IBD patients have varied.⁴⁵⁻⁴⁷ In one study, a lower abundance of mucosa-associated *Bifidobacterium* was found in IBD patients,³⁰ and in a meta-analysis, a lower abundance of *Bifidobacterium* in patients with active IBD was found compared with those in remission.³³ However, other studies have found a higher abundance of *B. bifidum* in IBD patients.^{45,46} As a result, the use of *Bifidobacterium* as a probiotic for IBD patients during the active disease status requires caution.⁴⁸ In the present study, a higher abundance of *B. bifidum* in fecal samples reflected more extensive disease status. The function of the bacteria can be different if the strain is different even if the species are the same, as we mentioned above. Therefore, the fact that bacterial function varies depending on the strain may have caused these results.

Additionally, *I. bartlettii* was a possible biomarker of not only moderate to severe UC but also left sided or extensive UC. Little is known regarding *I. bartlettii* except that it is involved in glucose metabolism and its abundance decreases in

patients taking metformin.^{49,50} Further studies on its relation to intestinal disease are needed.

We also attempted to identify microbial biomarkers for predicting clinical courses. In CD patients, the family *Lachnospiraceae* and species *R. gnavus* were significantly more abundant in patients with better prognosis. *Lachnospiraceae* is a butyrate-producing commensal bacteria, which induces regulatory T cells with anti-inflammatory functions.⁵¹⁻⁵³ Because *Lachnospiraceae* has been shown to have a negative association with CD,²⁵ this taxa is suggested to play an important role in disease prevention, and is a target for novel therapy.¹² *R. gnavus* is known to express beta-glucuronidase activity which induces the formation of toxic compounds in the colon causing local inflammation.⁵⁴ Its relation with disease activity and inflammation has previously been identified.⁵⁵ CD patients have a higher abundance of *R. gnavus* compared with healthy individuals, and patients with more extensive disease have a higher abundance of *R. gnavus* compared with those with isolated disease.^{25,32,55} It is unclear why 2 different taxa, which play opposite roles in the inflammatory cascade, were found as potential biomarkers for better prognosis; however, this finding may suggest a complex association between microbiota, inflammation, and disease prognosis.

There were several limitations to the study. First, it was not a longitudinal study. As the fecal samples were not collected serially, for example before and after treatments, it is difficult to identify serial changes in microbiota according to disease fluctuation. Second, the mean age and BMI were significantly lower in CD patients compared to the HC and UC patients, as the HC was selected based on UC patients. Several factors affecting the composition of gut microbiota such as diet, were also not controlled before collecting fecal samples. Third, extract DNA were stored at -80°C for a long time. However, recent study showed that long-term storage at -80°C only limited effect on the microbial community.⁵⁶ Fourth, we could not apply time-to-event methods to prognosis evaluation. Since the number of UC (13 patients) and CD (9 patients) patients evaluated as worse prognosis was relatively small, it was difficult to analyze them in consideration of the time when the event occurred. Finally, other inflammatory markers including fecal calprotectin and C-reactive protein were not investigated for the assessment of disease phenotypes. These results therefore need to be interpreted with caution. However, this study advances our knowledge as it identified the fecal microbiota related with the disease phenotypes and prognosis at the species level.

In conclusion, the fecal microbiota profile of IBD patients is different from HC and is characterized according to disease severity and extent. Several bacterial taxa have the potential to be used as biomarkers to assess disease severity and extent, which can be used to determine prognosis. These data may help discriminate disease phenotypes, predict clinical courses, and discover new therapeutic targets for IBD.

ADDITIONAL INFORMATION

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability Statement

Not applicable.

Author Contribution

Conceptualization: Choi CH, Lee SC. Methodology: Choi CH, Lee SC. Funding acquisition: Choi CH. Project administration: Shin SY, Kim Y, Kim WS, Moon JM, Lee KM, Jung SA, Park H, Huh EY, Kim BC. Writing original draft: Shin SY, Kim Y. Writing-review and editing: Choi CH, Lee SC. Approval of final manuscript: all authors.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (<https://www.irjournal.org>).

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