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Original Article

Comparison between Pediatric Crohn's Disease and Ulcerative Colitis at Diagnosis in Korea: Results from a Multicenter, Registry-Based, Inception Cohort Study

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Background/Aims: We aimed to compare the differences in pediatric Crohn's disease (CD) and ulcerative colitis (UC) at diagnosis in Korea.

Methods: This was a multicenter, registry-based, inception cohort study conducted at five centers in Korea between 2013 and 2017. Baseline demographics, clinical characteristics, and results from laboratory, endoscopic, radiologic examinations were compared between pediatric CD and UC patients who were <19 years old at diagnosis.

Results: A total 307 patients were included (227 CD [73.9%] and 80 UC [26.1%]). The male to female ratio was 2.49:1 for CD, and 1.49:1 for UC (p=0.019). Median age at diagnosis was 14.4 years (interquartile range, 12.4 to 16.2) for CD, and 14.4 years (interquartile range, 11.7 to 16.5) for UC (p=0.962). Hematochezia was the only dominant symptom in UC patients compared to CD patients (86.2% vs 30.8%, p<0.001). White blood cell counts, platelet counts, erythrocyte sedimentation rate, and C-reactive protein levels were significantly higher, and serum albumin level was significantly lower in CD patients than in UC patient. Anti-*Saccharomyces cerevisiae* antibody was positive in 44.5% and 16.2% of CD and UC patients, respectively (p<0.001), and antineutrophil cytoplasmic antibody was positive in 15.0% and 58.8% of CD and UC patients, respectively (p<0.001). Terminal ileal involvement was prominent in CD, while rectal involvement was more prominent in UC. Small bowel involvement and perianal perforating diseases were also more prominent in CD.

Conclusions: This is the first a multicenter study in Korea to compare the differences between pediatric CD and UC at diagnosis in Korea. A large-scale, national study is expected to better clarify these findings in the future. **(Gut Liver 2022;16:921-929)**

Key Words: Inflammatory bowel disease; Korea; Crohn disease; Ulcerative colitis; Child

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease with remissions and relapses that mainly involves the gastrointestinal (GI) tract.[1] The pathophysiology of IBD is not yet fully understood; however, environmental factors, microbial factors, and immune responses affect genetically susceptible individuals.[2,3]

The global prevalence of IBD is rapidly increasing. Although the prevalence of IBD was reported to be lower in Asian countries than in Western countries, it is increasing rapidly with the increase in industrialization.[4,5] According to a recent study, the global prevalence of IBD has increased from 3.7 million to 6.8 million from 1990 to 2017 despite the stable incidence in the Western countries due to the decrease in IBD-associated mortality and rising incidence rates in South America, Eastern Europe, Asia, and

Africa.[6,7] According to the studies in Korean cohorts, the adjusted prevalence of CD and UC in 2005 was 11.24 and 30.87 per 100,000, respectively, and the annual incidence of both CD and UC increased more than 100 times in the past 20 years.[8]

Approximately 25% of IBD patients are diagnosed in the first two decades of life, and the incidence and prevalence of pediatric IBD (PIBD) are also increasing in Asian countries.[9-12] From 2011 to 2016, the incidence of PIBD in the Daegu-Kyungpook province in Korea increased by 3.5 times.[13] Despite the increasing incidence, few multicenter studies have evaluated the characteristics of Korean PIBD patients. Previous multicenter studies that compared the clinical phenotypes of CD and UC involved a small number of patients and used the Montreal classification, with limited evaluation of the upper GI (UGI) tract.[13,14] Furthermore, no other studies have compared the laboratory findings between pediatric CD and UC at diagnosis. Therefore, we aimed to investigate the disease phenotype and characteristics of Korean pediatric CD and UC patients at diagnosis through a complete assessment of the entire GI tract and laboratory findings.

MATERIALS AND METHODS

1. Patients and study design

The Korean PIBD registry is a multicenter, inception cohort registry of PIBD patients in Korea. Five centers with tertiary care children's hospitals or university hospitals capable of diagnosing and managing PIBD patients participated in establishing this registry. Patients diagnosed with CD or UC based on the revised Porto criteria and aged <18 years at diagnosis, were included in this study.[15] Patients with IBD-unclassified (IBD-U) were included in the UC group due to the small number of patients and for simplicity. This registry comprises patients diagnosed with PIBD after 2013, and the analysis considered patients registered between 2013 and 2017.

Baseline demographic characteristics including sex, age at diagnosis, history of IBD among the first-degree relatives, history of surgery prior to the diagnosis, growth indicators, and parental height were investigated. The presence of major symptoms or signs at diagnosis, such as abdominal pain, diarrhea, hematochezia, vomiting, oral ulcers, fever, weight loss, and perianal lesions, was evaluated. Growth indicators including z-scores for weight-for-age, height-for-age, and body mass index-for-age were calculated using the 2017 Korean National Growth Charts for children and adolescents of the Korea Disease Control and Prevention Agency.[16]

Patients who underwent a complete diagnostic investigation of the GI tract according to the revised Porto criteria were included in this study. Data of the disease location and behavior were obtained through esophagogastroduodenoscopy (EGD), colonoscopy, and small bowel imaging such as magnetic resonance enterography, computed tomography, computed tomographic enterography, capsule endoscopy, or enteroscopy findings. Multiple biopsies from all segments of the GI tract were performed for histological evaluation. Disease phenotype at diagnosis was classified according to the Paris classification, and disease involvement was defined as the presence of ulcers, erosions, cobblestones, and/or stenosis from the esophagus to the second portion of the duodenum on EGD, and from the terminal ileum to the rectum on colonoscopy.[17] For the small bowel, disease involvement was defined based on the findings of small bowel imaging studies described above. Perianal fistulizing disease was confined to perianal fistulas and abscesses.

Laboratory investigations such as white blood cell count, hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, fecal calprotectin level, and positivity of antibody markers (anti-*Saccharomyces cerevisiae* antibody [ASCA] and perinuclear antineutrophil cytoplasmic antibody [pANCA]) at diagnosis of IBD were performed, and assessment of disease activity using indices such as pediatric Crohn's disease activity index and pediatric ulcerative colitis activity index was performed.[18,19]

2. Statistical analysis

For statistical comparison between CD and UC, the chi-square test or the Fisher exact test was used for categorical variables, and the Student t-test or the Wilcoxon rank-sum test was used for continuous variables. Comparative data for continuous variables are reported as median (interquartile range) or mean (standard deviation). Differences were considered statistically significant for p-values <0.05. Statistical analyses were performed using R version 3.2.3 (R development Core Team, 2015; R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org).

3. Ethics statement

This study was approved by the institutional review boards of all the participating institutions including Kyungpook National University Chilgok Hospital (IRB number: 2017-06-022), and the need for informed consent was obtained from patients and guardians who participated prospectively. We conducted this study in compliance with the principles of the Declaration of Helsinki.

RESULTS

1. Baseline characteristics

Between 2013 and 2016, 307 patients were registered in the Korean PIBD registry. Among 307 patients, 227 patients (71.9%) and 80 patients (28.4%) were diagnosed with CD and UC, respectively. Nine patients with IBD-U were included in the UC group. The baseline demographic variables of the patients are presented in Table 1.

There was no significant difference in the age at diagnosis between CD and UC patients (14.4 years for both, p=0.962). In the cohort, 71.4% of CD and 56.2% of UC patients were male, indicating significant male predominance in CD (p=0.019). There were significant differences between CD and UC patients in terms of height, weight, and body mass index z-score at diagnosis (z-score for height, –0.34 in CD and 0.07 in UC patients; z-score for weight, –0.93 in CD and –0.41 in UC patients; z-score for body mass index, –1.02±1.23 in CD and –0.63±1.16 in UC patients; p=0.007, p=0.001, and p=0.015, respectively), implicating significant delay in growth parameters in CD patients. There were no significant differences in mean average parental height between the two groups.

Although the number of patients with a history of surgical resection of the bowel at diagnosis was not significantly different between the two groups (p=1.000), history of perianal surgery at diagnosis was reported in 29.5% in CD and 0% in UC patients (p<0.001). Prevalence of a family history of IBD among first-degree relatives was not significantly different between the two groups (CD, 4.8%; UC, 5.0%; p=0.957).

2. Major symptoms or signs in PIBD patients at diagnosis

Major symptoms or signs of IBD at diagnosis are shown in Table 2. More than 50% of CD and UC patients presented with abdominal pain (CD, 76.2%; UC, 51.2%) and diarrhea (CD, 72.2%; UC, 67.5%) at diagnosis. CD presented with significantly higher abdominal pain than UC (p<0.001).

At diagnosis, the prevalence of oral ulcers (CD, 13.7%; UC, 3.8%; p=0.026), fever (CD, 20.3%; UC, 6.2%; p=0.007), weight loss (CD, 51.5%; UC, 22.5%; p<0.001), anal skin tag (CD, 15.9%; UC, 1.2%; p<0.001), perianal disease (CD, 38.3%; UC, 0%; p<0.001) was significantly higher in CD than in UC patients. In contrast, the prevalence of hematochezia was significantly higher in UC than in CD patients (UC, 86.2%; CD, 30.8%; p<0.001).

3. Laboratory findings of PIBD patients at diagnosis

Laboratory findings in IBD patients at initial diagnosis are presented in Table 3. The levels of serum markers for systemic inflammation such as white blood cell count (CD, 9,180/μL; UC, 8,245/μL; p=0.044), ESR (CD, 46 mm/hr; UC, 21 mm/hr; p<0.001), and CRP (CD, 2.6 mg/dL; UC, 0.2 mg/dL; p<0.001) were significantly higher and marked thrombocytosis was also noted in CD patients at diagnosis

Table 2. Symptoms and Signs of Pediatric IBD in Patients at Diagnosis

Variable	CD (n=227)	UC (n=80)	p-value
Abdominal pain	173 (76.2)	41 (51.2)	<0.001
Diarrhea	164 (72.2)	54 (67.5)	0.508
Blood-stained stool	70 (30.8)	69 (86.2)	<0.001
Vomiting	18 (7.9)	1 (1.2)	0.063
Oral ulcer	31 (13.7)	3 (3.8)	0.026
Fever	46 (20.3)	5 (6.2)	0.007
Weight loss	117 (51.5)	18 (22.5)	<0.001
Anal skin tag	36 (15.9)	1 (1.2)	<0.001
Anal fissure	19 (8.4)	2 (2.5)	0.126
Perianal fistula/abscess	87 (38.3)	0	<0.001

Data are presented as number (%).
IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

Table 1. Demographics of Newly Diagnosed Pediatric IBD Patients

Variable	CD (n=227)	UC (n=80)	p-value
Male sex	162 (71.4)	45 (56.2)	0.019
Ratio of male:female	2.49:1	1.49:1	
Age at diagnosis, yr	14.4 (12.4 to 16.2)	14.4 (11.7 to 16.5)	0.962
Height Z-score	–0.34 (–1.14 to 0.48)	0.07 (–0.83 to 0.79)	0.007
Weight Z-score	–0.93 (–1.91 to –0.14)	–0.41 (–1.27 to 0.41)	0.001
BMI Z-score	–1.02±1.23	–0.63±1.16	0.015
Paternal height, cm	171.9±5.2	172.9±3.8	0.436
Maternal height, cm	160.0 (158.0 to 163.2)	162.0 (158.5 to 164.5)	0.481
History of bowel resection	1 (0.4)	0	1.000
History of perianal surgery	67 (29.5)	3 (3.8)	<0.001
Family history of IBD	11 (4.8)	4 (5.0)	0.957

Data are presented as number (%), median (interquartile range), or mean±SD.
IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; BMI, body mass index.

(CD, 450×10^3/μL; UC, 354.5×10^3/μL; p<0.001). Albumin level was significantly lower in CD patients, although it was within the normal range in both groups (CD, 3.8 g/dL; UC, 4.2 g/dL; p<0.001).

The rate of positivity for ASCA was 44.5% in CD (n=101) and 16.2% in UC (n=13) (p<0.001), and that for pANCA was 15.0% in CD (n=34) and 58.8% in UC (n=47) (p<0.001). Elevation of fecal calprotectin was noted in both groups, and the difference was not significant (CD, 1,000 mg/kg [interquartile range, 431 to 1,338] vs UC, 1,000 mg/kg [interquartile range, 351 to 1,800]; p=0.525).

4. Disease location and extent

A complete evaluation of the entire GI tract was performed in all the patients at diagnosis, and the location, behavior, and extent of the disease are summarized in Table 4.

Esophageal involvement was seen in 8.4% in CD and 2.5% in UC patients on EGD, showing no significant difference between the groups. However, gastric involvement was observed in 36.6% in CD and 12.5% in UC patients (p<0.001).

Table 3. Laboratory Findings at Diagnosis

Variable	CD (n=227)	UC (n=80)	p-value
WBC, /μL	9,180 (7,445–11,260)	8,245 (6,425–10,695)	0.044
Hemoglobin, g/dL	11.9 (10.6–13.1)	12.1 (10.4–13.6)	0.485
Hematocrit, %	37.2 (33.9–40.0)	36.6 (32.8–41.1)	0.791
Platelet, ×10^3/μL	450.0 (350.0–522.5)	354.5 (271.5–445.0)	<0.001
ESR, mm/hr	46.0 (27.0–71.0)	21.0 (9.0–36.5)	<0.001
CRP, mg/dL	2.6 (0.9–5.5)	0.2 (0.0–0.7)	<0.001
Albumin, g/dL	3.8 (3.5–4.1)	4.2 (3.9–4.6)	<0.001
Fecal calprotectin, mg/kg	1,000 (431–1,338)	1,000 (351–1,800)	0.525
ASCA (+)	101 (44.5)	13 (16.2)	<0.001
pANCA (+)	34 (15.0)	47 (58.8)	<0.001

Data are presented as median (interquartile range) or number (%).
CD, Crohn's disease; UC, ulcerative colitis; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASCA, anti-*Saccharomyces cerevisiae* antibody; pANCA, perinuclear antineutrophil cytoplasmic antibody.

Table 4. Location and Behavior of CD and Extent of UC at Diagnosis

Variable	CD	UC	p-value
Esophagogastroduodenoscopy			
Esophagus	19 (8.4)	2 (2.5)	0.126
Stomach	83 (36.6)	10 (12.5)	<0.001
Duodenum	47 (20.7)	6 (7.5)	0.012
Non-caseating granuloma	5 (2.2)	-	NA
Small bowel and perianal evaluation			
Duodenum	3 (1.3)	0	0.710
Jejunum	31 (13.7)	2 (2.5)	0.010
Proximal ileum	33 (14.5)	1 (1.2)	0.002
Distal ileum	84 (37.0)	2 (2.5)	<0.001
Terminal ileum	151 (66.5)	8 (10.0)	<0.001
Perianal fistula/abscess	87 (38.3)	0	<0.001
Colonoscopy			
Terminal ileum	141 (62.1)	13 (16.2)	<0.001
Caecum	138 (60.8)	39 (48.8)	0.081
Ascending colon	139 (61.2)	43 (53.8)	0.299
Transverse colon	135 (59.5)	46 (57.5)	0.860
Descending colon	130 (57.3)	50 (62.5)	0.493
Sigmoid colon	135 (59.5)	52 (65.0)	0.460
Rectum	119 (52.4)	67 (83.8)	<0.001
Non-caseating granuloma	88 (38.8)	-	NA
Endoscopic scores			
SES-CD	20 (9–27)	-	NA
Mayo endoscopic score	-	2 (2–3)	NA

Data are presented as number (%) or median (interquartile range).
CD, Crohn's disease; UC, ulcerative colitis; SES-CD, simple endoscopic score for CD; NA, not applicable.

Duodenal involvement was also significantly higher in CD (CD 20.7% vs UC 7.5%, p=0.012). UC patients with esophageal and duodenal involvement also showed gastric involvement. Among UC, two patients showed esophageal, gastric, and duodenal involvement and four patients showed gastric and duodenal involvement. All of the patients with UC who had UGI tract involvement had erosions, and among them 50.0% (1/2), 60.0% (6/10), and 66.7% (4/6) had ulcers. Of the patients with CD who underwent a biopsy during EGD, 2.2% showed non-caseating granuloma.

On small bowel imaging, there was a significant difference in the involvement of each segment of the small intestine and the presence of perianal lesions between CD and UC patients: 13.7% of the jejunum, 14.5% of the proximal ileum, 37.0% of the distal ileum, and 66.5% of the terminal ileum in CD patients were involved, whereas 2.5% of the jejunum, 1.2% of the proximal ileum, 2.5% of the distal ileum, and 10.0% of the terminal ileum in UC patients were involved (p=0.010, p=0.002, p<0.001, and p<0.001, respectively). Perianal fistula and abscesses were found in 38.3% of CD patients at diagnosis but not found in any UC patients (p<0.001).

On colonoscopy, the involvement of the terminal ileum in CD and UC patients was 62.1% and 16.2%, respectively; these were similar to the results seen on small bowel imaging. We found that 60.8%, 61.2%, 59.5%, and 57.3% of the cecum, ascending colon, transverse colon, and descending and sigmoid colon were involved in CD, respectively, whereas 48.8%, 53.8%, 57.5%, 62.5%, and 65.0% of the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon were involved in UC, respectively. All segments of the colon did not show significant differences in the extent of involvement between the two disease groups except for the rectum, which showed an extent of 52.4% in CD and 83.8% in UC (p<0.001). Of the biopsied specimens of CD patients, 38.8% showed non-caseating granuloma. The median simple endoscopic score for CD was 20, and the median Mayo endoscopic score was 2.

5. Disease phenotype and activities at diagnosis according to the Paris classification

The disease phenotype and behavior based on the Paris classification and disease activities are shown in Table 5. Among the 227 patients with CD, 77.1% of patients (n=175) were categorized as A1b, 15.0% (n=34) as A2, and 7.9% (n=18) as A1a. For the luminal disease behavior, 74.0% of patients (n=168) was categorized as B1, 4.8% (n=11) as B2, 20.3% (n=46) as B3, and 0.9% (n=2) as B2B3. For perianal lesions, 108 of 227 patients (47.6%) were defined as having perianal disease modifiers.

Regarding the location of disease, almost two-thirds of patients (67.4%) had L3, 13.7% (n=31) had L1, and 14.5% (n=33) had L2 involvement. Lower GI involvement was not seen in 4.4% of CD patients. In the analysis of the UGI tract involvement, 30.4% of patients (n=69) were categorized as L4a and 27.3% (n=62) as L4b, and 16.3% (n=37) as L4ab. UGI involvement was not seen in 26.0% (n=59) of CD patients.

In UC patients, 53.8% (n=43) were categorized as E4 in terms of extent, 27.5% (n=22) as E1, 11.3% (n=9) as E2, and 7.5% (n=6) as E3. Regarding disease activity, the median pe-

Table 5. Paris Classification and Disease Activity Indices

Classification	Value
Crohn's disease (n=227)	
Age at diagnosis	
A1a	18 (7.9)
A1b	175 (77.1)
A2	34 (15.0)
LGI involvement and location	
L1	31 (13.7)
L2	33 (14.5)
L3	153 (67.4)
None	10 (4.4)
UGI involvement and location	
L4a	69 (30.4)
L4ab	37 (16.3)
L4b	62 (27.3)
None	59 (26.0)
Luminal disease behavior	
B1	168 (74.0)
B2	11 (4.8)
B3	46 (20.3)
B2B3	2 (0.9)
Perianal disease modifier	
No	119 (52.4)
Yes	108 (47.6)
PCDAI	37.5 (30.0–47.5)
Ulcerative colitis (n=80)	
Extent	
E1	22 (27.5)
E2	9 (11.3)
E3	6 (7.5)
E4	43 (53.8)
PUCAI	40 (25–55)

Data are presented as number (%) or median (interquartile range). The classification in the table is as follows. A1a: age <10 yr, A1b: 10 to <17 yr, A2: age ≥17 yr. L1: distal 1/3 ileum±limited cecal disease, L2: colonic disease, L3: ileocolonic disease, L4a: upper disease proximal to ligament of Treitz, L4b: upper disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum, L4ab: upper disease involvement in both L4a and L4b. B1: non-stricturing, nonpenetrating behavior, B2: stricturing behavior, B3: penetrating behavior, B2B3: both B2 and B3. E1: ulcerative proctitis, E2: left-sided UC (distal to splenic flexure), E3: extensive (hepatic flexure distally), E4: pancolitis (proximal to hepatic flexure).
UGI, upper gastrointestinal; PCDAI, pediatric Crohn's disease activity index; PUCAI, pediatric ulcerative colitis activity index.

diatric Crohn's disease activity index and pediatric ulcerative colitis activity index scores were 37.5 and 40, respectively.

DISCUSSION

The annual incidence of PIBD in the Korean population is increasing, and the age at diagnosis of PIBD is decreasing. However, there are few multicenter studies among Korean patients with PIBD. To our knowledge, this is the first multicenter study involving the largest number of patients from the Korean PIBD registry with a complete investigation of the entire GI tract and laboratory data that has compared the characteristics between CD and UC.

The incidence and prevalence of IBD in Korea have increased over time; the incidence of CD has particularly shown a steep increase in previous studies based on data from the Korean PIBD cohort study.[8,13,14,20-22] Hong *et al.*[13] showed that the mean ratio of newly diagnosed CD to UC was 4:1 in Kyungpook province, which has increased from 3.5:1 to 5:1 over a 5-year period. In our registry, the numbers of CD and UC patients were 227 and 80, respectively; thus, the number of CD patients was 2.8 times that of UC patients. Although the difference could be due to the sample size, regional biases, institutional biases, and study durations, the higher prevalence of CD than that of UC in the pediatric population is similar to that reported in the EUROKIDS study (59% vs 32%).[23,24]

In our study, significant male predominance in the prevalence of CD compared to that in UC was noted. Previous studies, including both single-center and some multicenter studies, also reported male predominance in the Korean pediatric CD patients.[13,14,20] There are other studies that reported male predominance in the Asian pediatric CD population, whereas no difference in the prevalence between males and females was seen in the EUROKIDS study.[23,25,26] Hong *et al.*[13] explained the male predominance being due to the skewed sex ratio of the province during the enrolment period; our study overcomes this limitation and is more representative of the prevalence since it is a nationwide multicenter study. The male predominance in pediatric CD in the Asia-Pacific region might be due to ethnicity or environmental influences, since these regions share similar environmental and genetic factors.[25-27]

The mean age at diagnosis was 14.4 years for both CD and UC patients. A previous study reported a younger age at diagnosis of IBD in Korea, being 12.0 years for CD and 12.6 years for UC. This might be because of the smaller sample size or the change in age groups with time.[20] More recent studies involving larger number of patients with PIBD in Korea, reported a higher age at diagnosis, being 15.3 years for CD and 15.8 years for UC, which was consistent with our data.[14] Meanwhile, data from the EUROKIDS registry have shown a median diagnosis age of 12.5 years for CD and 11.6 years for UC.[23,24] While all centers in this study were responsible for new patients aged <18 years, approximately one-third of the centers participating in the EUROKIDS cohort reported that new patients aged >15 years were always referred to an adult gastroenterologist.

Although the majority of pediatric CD patients present with abdominal pain, diarrhea, and weight loss at diagnosis, more than one-third had perianal disease. In a previous study, there was no statistical difference in abdominal pain and weight loss, but abdominal pain and weight loss were higher in CD than in UC patients.[20] A higher prevalence of perianal disease in the Korean and Japanese PIBD population than in the Western cohorts has been reported in many studies, and our study confirmed the previous data.[20,22,26,28-30] In this study, 29.5% of pediatric CD patients had undergone perianal surgery before diagnosis, which indicates that there are many patients in whom the primary clinical manifestation is perianal lesions. Clinicians should be aware of the increasing prevalence of PIBD among Korean adolescents, and their initial clinical manifestation might not always be abdominal pain, diarrhea, and weight loss.

Compared to the previous studies, our study analyzed the laboratory data at diagnosis to compare the serologic markers between CD and UC patients, which makes our study more meaningful. Significantly higher ESR and CRP levels were observed in CD patients than in UC patients, while fecal calprotectin was elevated in both groups. Elevation of CRP in CD patients than in UC patients was also reported in a previous study; however, it could not distinguish CD from UC.[31] Although CRP is an indicator of inflammation in IBD, several studies show that the sensitivity of CRP for IBD might be limited, even in those with active disease.[32,33] Alper *et al.*[33] reported that up to 28% of CD patients and 42% of UC patients showed normal ESR and CRP at diagnosis in a retrospective study among 135 children with IBD. This suggests that elevation of serologic inflammatory markers might not help distinguish between CD and UC. However, the degree of inflammation and transmural inflammation in CD might lead to elevation of serum inflammatory markers, compared to that in UC, in which the inflammation is limited to the mucosa. However, no significant relationship between the disease activity and elevation of ESR and CRP was seen; further studies are necessary to understand the significance of elevated serologic inflammatory markers in UC. Forty-four points five percent of patients with pediatric CD were ASCA positive and 58.8% of patients with UC were pANCA positive, which was comparable to that

reported previously. Birimberg-Schwartz *et al.*[34] confirmed 40% of European pediatric CD patients were ASCA positive and 64% of UC patients were pANCA positive. They also showed 30% pANCA positivity in CD and 6% ASCA positivity in UC. The rate of positivity of pANCA in CD is lower and that for ASCA in UC is higher in our cohort than those reported in previous studies, which might be due to genetic differences.

The majority of the Korean CD patients showed ileocolic disease (L3); fewer had colonic involvement (L2), while more patients had UGI involvement than that reported in the EUROKIDS study, which showed a predominance of L2 over L1 (27% vs 16%); however, our study did not show significant differences between the two groups.[23] In a previous study, 79.3% of 594 Korean CD patients showed L3 involvement, and 25.8% showed UGI involvement, which was in line with our study.[21] Recent data from a Japanese cohort study on PIBD also reported less colonic and more UGI, ileocolic, and perianal involvement. These differences between EUROKIDS and other studies might be due to the extensive small bowel investigations performed in these studies. In subgroup analysis of EUROKIDS regarding ethnicity, the Asian group did not show significant prevalence in L4a group. However, more abundant UGI involvement was reported in some other Asian cohort studies, suggesting that the environmental factors such as food culture combined with a similar genetic predisposition may affect the location of the disease.

In our study, 12.5% of pediatric UC patients showed UGI involvement. Moreover, 16.2% of patients also had backwash ileitis, and 16.2% had rectal sparing during the first presentation. More than half the patients presented with pancolitis (E4) at first diagnosis, and ulcerative proctitis (E1) was the next common presentation. Previous data about pediatric UC showed that 43% of patients had pancolitis, which was the most prevalent presentation; however, left-sided colitis (36%) was also prevalent.[20] Another recent study from Daegu-Kyungpook province showed that 58.4% of patients belonged to E4 category and 27.5% to E1, which was consistent with our study.[13] The differences between the two Korean UC cohorts might be due to the small sample size in the first study. However, since the first study was conducted more than 10 years ago, the difference in the periods of the studies and environmental factors associated with the etiology of UC might have been the cause of data discrepancy. In a recent study conducted in Japan, 76% of patients were categorized as E4 followed by left-sided colitis (E2) seen in 12.3% of the patients.[26] EUROKIDS also showed that 78% of patients belonged to the E4 category, while the proportion of patients in E1 (5%) was small.[24] Moreover, 4% had UGI involvement, and 10% had backwash ileitis, which was representative of atypical UC. Pediatric UC shows a higher predominance of E4 over other locations; however, the Korean cohort shows a higher predominance of E1 than that in other countries, which might be due to ethnic differences. However, since the Japanese PIBD cohort showed the distribution of disease location similar to that in EUROKIDS, we can conjecture that there might be other factors besides environment and ethnicity.

At diagnosis, most CD or UC patients showed moderate degree of disease, while the mean endoscopic score showed severe disease in CD patients and moderate disease in UC patients. This supports the previous reports about the discrepancy between the endoscopic score and clinical disease activity, and re-emphasizes that disease activity always does not reflect the mucosal status.

This study has some limitations. First, since the Korean PIBD registry is not a population-based cohort registry, there is a risk of selection bias. However, the five centers involved in this study are major centers in Korea with pediatric gastroenterologists and manage approximately half of PIBD patients in Korea. Hence, the data about the phenotypes, laboratory, and endoscopic findings of patients with PIBD in this study might reflect the population-based data. Second, the reports of the endoscopic findings and diagnosis of IBD were not centralized and relied on the assessment of the pediatric gastroenterologists who participated in the study. However, the data can be considered reliable since the participating centers are deemed to be capable of diagnosing IBD based on imaging and endoscopic findings and managing such patients. Third, due to the small number of patients with IBD-U, they were included into the UC group. Future studies with larger number of patients are required to better delineate the characteristics of IBD-U in pediatric patients in Korea.

In conclusion, this is the first multicenter study in Korea to compare the differences between pediatric CD and UC at diagnosis in Korea. Future studies involving a larger number of patients with the analysis of gene expression profiles, disease phenotypes, and ethnicity with long-term follow-up are necessary. Understanding the interaction between genetic predisposition and phenotypes might facilitate a precision approach for each PIBD patient and achieve modification of the natural disease course.

CONFLICTS OF INTEREST

This study was supported by Eisai Korea, Inc. Except for that, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

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